THE ROYAL SOCIETY
OF CANADA

HEALTH EFFECTS OF LEAD

EDITED BY
MARCUS C.B. HOTZ

THE COMMISSION ON LEAD IN THE ENVIRONMENT

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PREFACE

This is one of three complementary volumes of scientific papers that the Royal Society of Canada's Commission on Lead in the Environment used extensively in preparing its final report, Lead in the Canadian Environment: Science and Regulation.

The present volume deals with the health effects of lead. The second contains papers dealing with the pathways taken by lead in its movement through the environment towards human targets. In addition to material presented at the Commission's workshops, both volumes contain syntheses of the matters under discussion, written by their respective editors or by individual Commissioners. The third volume is a technical appraisal of the health effects and industrial and engineering problems inherent in the alternative lead-free ways of matching fuels to engines.

Of the papers presented here, numbers 1 (the editorial overview, by M.C.B. Hotz), 6, 17, 18, 19 and 22 were prepared by Commissioners, or by consultants and professional staff. They are syntheses intended to supplement the final report of the Commission. The remaining papers were presented at workshops held in Toronto on February 18, 1985 and in Ottawa on March 29 and 30, 1985, or one arranged by ILZRO (subsequently reviewed by the authors in some cases).

The Society is grateful to all the individual contributors whose views are expressed in these documents. They are also entitled to all the credit due for their labours.

F. Kenneth Hare
Chairman

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ABBREVIATIONS

AA : atomic absorption
AAS : atomic absorption spectrophotometry
ALA : -aminolaevulinic acid
ALAD : -aminolaevulinic acid dehydratase
ALAP : ALA in plasma
ALAU : ALA in urine
ASR : aldosterone secretion rate
ASV : anodic stripping voltammetry
ATP : adenosine triphosphate
BMI : body mass index
cAMP : cyclic-AMP
CASAC : Clean Air Scientific Advisory Committee
CDC : US Centers for Disease Control
CEC : Commission of the European Communities
CHS : Canada Health Survey
CI : confidence interval
CNS : central nervous system
CV : coefficient of variation
CVSF : conduction velocity fo slow motor fibres
DMLP : distal motor latency period
EC : Environment Canada
EDTA : ethylenediamine tetraacetic acid
EEG : electroencephalogram
EPA : US Environmental Protection Agency
FEP : free erythrocyte protoporphyrin
GFAAS : graphite furnace atomic absorption spectrophotometry
Hb : hemoglobin
IDMS : isotope dilution mass spectrometry
IBR : infant behaviour record
LLD : lower limit of detection
MAP : motor action potential
MCV : motor conduction velocity
MDI : Mental development index
MLCK : myosin light-chain kinase
MMCV : maximal motor conduction velocity
MNCV : maximal nerve conduction velocity
NAA : neutron activation analysis
NAAQS : National Ambient Air Quality Standard
NAS : US National Academy of Sciences
NCV : nerve conduction velocity
NCHS : US National Center for Health Statistics
NHANES II: Second National Health and Nutrition Examination Survey
NIH : National Institutes of Health
PbB : blood lead
PHA : phytohemagglutinin
Pi : inorganic phosphorus
PRA : plasma renin activity

PROM : premature rupture of membranes
PTDI : provisional tolerable daily intake
PTH : parathyroid hormone
Py-5-N : pyrimidine-5-nucleotidase
SAP : sensory acton potential
SAS : Statistical Analysis System
SCE : sister chromatid exchange
SCr : serum creatinine
SCV : sensory conduction velocity
SD : standard deviation
SES : soico-economic status
SIDS : sudden infant death syndrome
SMR : standard mortality ratio
STPF : stabilized temperature platform furnance
TPN : total parenteral nutrition
TWA : time-weighted average
WHO : World Health Organization
ZPP : zinc protoporphyrin

1. LEAD AND HEALTH--AN EDITORIAL OVERVIEW

Marcus C.B. Hotz

Commission on Lead in the Environment
Toronto

The toxicity of lead to lead workers and miners has been recognized for almost as long as the metal has been mined and used, but it is only in recent years that attention has been focussed on low-level chronic exposures. There is no doubt that the lead burden of the general population is now much greater than in pre-industrial times (Nriagu, p. 61). A great deal of research has been done on the health effects of lead but, despite the fact that it is one of the most intensively studied toxic materials, controversy still rages about some aspects of its impact on biological processes.

The revolution in analytical techniques over the past two decades now allows scientists to measure levels of lead which were previously undetectable in biological fluids and tissues. As analytical technology has advanced, so has the realization that lead affects metabolic and other processes, firstly at blood lead levels below those at which clinical symptoms of toxicity (plumbism) are visible, and latterly even at those very low levels at which the susceptibilities of individual subjects become a matter of concern. Originally 'safe' exposure levels for general populations were defined on the basis of the occupational exposures deemed safe for workers (80-100 μg/dL); now we can observe effects on heme biosynthesis at levels an order of magnitude lower. The US Centers for Disease Control and the regulatory agencies of other countries have progressively lowered the 'level of health-related concerns' in children from 40 μg/dL of blood to 25 μg/dL over a period of 10 years. They are under pressure to lower it still further, but the inexpensive and widely used method of identifying children at risk by measuring free erythrocyte protoporphyrin (FEP) is unreliable below 25 µg/dL. Despite the large body of convincing evidence that has now accumulated, McCabe (p. 195) still questions whether many of the effects observed are really acute biochemical effects, or are merely "normal responses". He believes that the interaction of lead with enzyme processes "needs further work to differentiate simple biological changes from adverse health effects."

As analytical technology for measuring lead in foods and body tissues has improved, it has been plagued by a lack of consistency among the methods used and the analyses done by different laboratories. These problems are only now being overcome through more precise methodology and interlaboratory comparison programmes. Much of the older work hence cannot be validly used to identify trends. Loose terminology for lead exposure has also proved to be a problem, particularly in the light of the ever lower 'levels of concern' that are clinically asymptomatic. The levels regarded by some authors as being 'high' may be 'low' to others, depending in large measure on the range of blood lead levels in different populations, often in different regions or countries. Dabeka (p. 181) describes the problems of inconsistency in analysis for lead in foodstuffs.

Most of the lead intake is eliminated from the body fairly rapidly, but the appreciable fraction that is absorbed is transported by the blood to various organs, notably the liver, kidney and brain. The ultimate 'sink' is the skeleton. There are two usual approaches to measuring the level of lead in the body. One approach measures the concentration of lead in a body fluid, typically blood or urine, which may be a good indicator of more or less recent exposure (30-60 days). Longer-term exposure may be estimated by analysis of tissues, such as teeth, bone or hair. Hair is complicated by surface contamination, and shed deciduous teeth are by their natur[illegible] a once-only measurement; bone biopsy is generally inappropriate.

The other approach is to measure the biologically available lead indirectly through its effect on certain metabolic processes. For example, the concentration of a heme precursor (protoporphyrin) in blood or urine, or the inhibition of the production of δ-aminolaevulinic acid dehydratase (ALAD) in blood may be measured. These methods are not affected by skin contamination in sampling; lead in capillary blood may be 6-10 μg/dL higher than in venous blood (Mahaffey et al., 1982; Ryu et al., 1985). The British Royal Commission on Environmental Pollution (1983) cautioned, however, that factors other than lead can result in increased erythrocyte protoporphyrin levels. Also, Bush (1982) noted that the correlations between blood lead and erythrocyte protoporphyrins are not very good for children under 3 years of age.

ALAD and FEP methods, however, can only be effectively used to screen populations at somewhat high levels of blood lead equivalent to or greater than 40 and 25 μg/dL, respectively. Thus at the lower levels more widely seen in the population (<15 μg/dL), these methods are prone to give false negative results which cannot be verified as easily as false positives. Direct measurement of lead in blood is thus the most widely used approach, usually by anodic stripping voltammetry (ASV) or atomic absorption spectrophotometry; these methods are described and assessed by Hammond (p. 27), Nantel (p. 79) and Hamilton and Farant (p. 41). The most accurate (and very costly) method is isotope dilution mass spectroscopy. This is often used as the standard for comparison of other methods, and Hammond believes that it should be more extensively used as the standard of 'truth'. Whichever methods are used, it is important to remember that the steady-state blood level that is reached in chronic exposure cannot be correlated with past exposures, which may have been higher, or which occurred during the particularly sensitive period of early development (Rice, p. 247).

The developing physiological systems of children are more sensitive to lead and are at greater risk, especially in very young children, than those of adults. Children, however, have a higher intake of lead resulting from greater hand-to-mouth activity and exposure to contaminated dusts and soils. Dabeka (p. 181) reviews the significance of dietary lead intakes. Children's intake also tends to be higher on a body-weight basis because of higher requirements for calories, fluid and air (Mahaffey and Michaelson, 1980), but they absorb between 42 and 53% of ingested dietary lead compared with 7-15% in adults (Chamberlain et al., 1978; Ziegler et al., 1978; Rabinowitz et al., 1980; Beloian, 1985). This high level of intake can be exacerbated by certain dietary deficiencies (Mahaffey and Michaelson, 1980; Heard and Chamberlain, 1982; Mahaffey, 1985) and, of course, by exposures resulting from living conditions and socio-cultural factors. These factors include lead water piping, proximity to smelters and major roadways, play and eating habits, family hygiene and flaking lead paint in substandard housing. Paint has been responsible for many cases of lead toxicity treated in pediatric hospitals in older cities, particularly in the United States. Rosen (p. 203) draws attention to the significance of paint in New York, as does Hammond (p. 27) in Cincinnati, but Ellis (1985) believed housing maintenance in Toronto in particular and Canada in general to be superior. He cited data from the South Riverdale area of Toronto implicating paint in the housing of less than 1% of children with blood lead levels greater than 20 μg/dL.

Lead has been shown to interfere with a number of metabolic processes, although the exposures at which most of these effects have been positively identified generally correspond to blood lead levels of 25 μg/dL or greater.

So much work has been done on the impact of lead on biological systems that it is not surprising to find connecting threads--if not a continuum--leading from subcellular effects through metabolic processes to functional impairment and the clinical symptoms of lead toxicity. The primary connecting link appears to be the hematopoietic system, which can be followed all the way from heme biosynthesis in cell mitochondria, through documented effects on the central and peripheral nervous systems, ultimately to impairment of kidney and liver processes and anemia at toxic blood lead levels.

Lead affects the biosynthesis of heme, which is required for the formation of hemoglobin, the erythrocyte respiratory pigment through which the blood transports oxygen to the tissues, as well as several related hemoproteins such as cytochromes, the mitochondrial respiratory pigments that control cellular energetics. As a result, unusable intermediates accumulate and the availability of heme is reduced. Lead has been shown to interfere with the first two steps of the heme synthesis process, first increasing the formation of δ-aminolaevulinic acid (ALA), and then inhibiting its condensation by the enzyme ALA-dehydratase (ALAD), so that the level of ALA in the body fluids increases. These effects have been reported at blood lead levels as low as 10-15 μg/dL in both adults and children (Hernberg and Nikkanen, 1970; Roels et al., 1975), although marked acceleration in the rate of urinary ALA excretion occurs only in the 25-40 μg/dL range (Meredith et al., 1978; Moore et al., 1980). ALA elevation has been observed in the liver, kidney and spleen, and at higher levels in the developing brains of young children than in adults.

The last stage of heme biosynthesis is also inhibited by lead. This involves the insertion of iron into protoporphyrin by the enzyme ferrochelatase, leading in turn to the accumulation of protoporphyrins in the mitochondria. Without iron, the protoporphyrins are incapable of performing their respiratory functions, but they are nevertheless incorporated into the developing erythrocytes instead of hemoglobin. The erythrocyte protoporphyrin rapidly chelates zinc to form a very stable inactive zinc protoporphyrin, which persists for the life of the cell (about 4 months) (Lamola and Yamane, 1974; Lamola et al., 1975). It is noteworthy that the ultimate 'sink' of lead is in bone, so that the marrow, with its developing erythrocytes, is likely to be heavily exposed to lead, perhaps at levels higher than in the circulating blood. Piomelli and his co-workers (1982) found that an exponential increase in the concentration of erythrocyte protoporphyrin occurred in children at blood lead levels above 15-18 µg/dL. They suggested that this value might indicate a threshold for lead damage, noting that this level is within the so-called 'normal' range of blood lead.

Much of the heme synthesized in the liver is used to make the P450 cytochrome oxidases. Production of these hemoproteins is induced by many drugs and toxins which the cytochromes then detoxify by hydroxylation. Liver cytochrome P450 levels are depressed in adults occupationally exposed to lead and in chronically exposed children with blood lead levels in excess of 40 µg/dL, who consequently have lower drug detoxification rates. Children who do not have elevated erythrocyte protoporphyrin levels or other evidence of interference with heme synthesis would not, however, be at risk from inhibition of detoxification. On the other hand, a small proportion of people are genetically poor metabolizers of certain drugs due to a hydroxylation anomaly that has been traced to a defect in at least one hepatic P450 cytochrome (Barbeau et al., 1985). A lead-caused cytochrome reduction superimposed on this condition might well have a more severe effect on such a sensitive person.

Further evidence for impacts on cytochrome P450 activity in the liver is given by the inhibition of urinary excretion of 6β-hydroxycortisol in children with high tissue lead burdens, as shown by ethylenediaminetetraacetic acid (EDTA) provocative testing, and blood lead levels in excess of 40 µg/dL (Saenger et al., 1984). 6β-hydroxycortisol is a P450-mediated metabolite of cortisol, and its inhibition appears to be a consequence of lead's effect on heme biosynthesis.

The hormonal metabolite 1,25-dihydroxyvitamin D is involved in bone mineralization, the intestinal absorption of phosphorus and the absorption and homeostasis of calcium, an essential element in a number of neurological, pancreatic and other response mechanisms (Rosen, 1983). 1,25-dihydroxyvitamin D is produced in kidney mitochondria by a P450 cytochrome-mediated process, and is depressed at blood lead levels of about 33 µg/dL, at which erythrocyte protoporphyrin accumulation becomes noticeable (Rosen et al., 1980, 1981). The involvement of the hemoprotein cytochrome and the appearance of erythrocyte protoporphyrin as its action is inhibited might indicate a lead-originated interference with heme production. Decreased calcium, depression of bone mineralization and increased levels of parathyroid hormone have been observed at blood lead levels in excess of 62 µg/dL, although there have been suggestions of effects below 20 µg/dL. These interpretations have been strongly criticized by DeLuca (1985) in a critique provided to the US Environmental Protection Agency's Clean Air Science Advisory Committee. He contended that it is premature to conclude that increased lead specifically suppresses the vitamin D hormone system, and that several of these assertions are based on 'over-extrapolations' from in vitro experiments. Sherlock et al. (1985) found no correlation between plasma 1,25-$(OH)_2$-vitamin D metabolite and blood lead at lead levels below 25 µg/dL, although children of Asian origin had significantly lower metabolite plasma levels than those of British origin.

The hemolytic anemia and other effects observed in lead intoxication are similar to those noted in patients with a genetic deficiency of pyrimidine-5'-nucleotidase (Paglia and Valentine, 1975; Paglia et al., 1975, 1977; Buc and Kaplan, 1978), an erythrocyte enzyme that suppresses the formation of pyrimidine nucleotides in favour of the purine nucleotides which are precursors of ATP. Lead inhibits the action of this enzyme, although children with blood lead levels below 30 µg/dL had normal levels of enzyme activity and virtually pyrimidine nucleotide-free erythrocytes (Angle et al., 1982).

Lead appears to be selectively absorbed by cells of the central and peripheral nervous systems, especially during their early development. As a neurotoxin, it appears to affect sodium and calcium metabolism and to inhibit the neuronal enzymes. Accumulation of the heme precursor ALA is also believed to be linked to some of the clinical and biochemical effects of lead intoxication. Acute encephalopathy (degenerative brain disease) occurs in adults at 100-120 µg/dL (Chisolm, 1965; NAS, 1972) and in the most susceptible children at 80-100 µg/dL (EPA, 1977); peripheral nerve damage is usually found in occupationally exposed adults at levels greater than 40 µg/dL (Haenninen et al., 1979; Zimmerman-Tansella et al., 1983). Chronic exposures to so-called 'low-level' exposures (50-80 µg/dL) in lead workers have been implicated in oculomotor dysfunction, impaired hand dexterity, memory loss, nervousness and changes in reaction time and IQ scores. Of greater concern are reports of some of these effects in the 27-50 µg/dL range (Haenninen et al., 1978; Mantere et al., 1982).

Lead is rapidly taken up by the brain, particularly in the hippocampus, cerebral cortex and certain non-neuronal cells important in blood-brain barrier functions. It tends to have a long residence time in the brain. The areas in which lead is deposited and the time factor are consistent with some of the behavioural changes that have been reported, and with the persistence of certain electrophysiological effects which are not, however, well understood. The behavioural effects reported in these studies are difficult to evaluate, but recent results from prospective studies based on umbilical cord blood lead levels do suggest that blood lead levels of about 15 µg/dL during the first 2 years of life may indeed have a small impact on mental development. This is treated more fully by Dietrich (p. 269).

It may be possible that some of this selective absorption by brain tissue may arise from inhaled lead taken up by the blood in the lungs, part of which is transported via the pulmonary vein and aorta directly to the brain without being exposed to cytochrome detoxification in the liver (Barbeau, 1986). If this is so, inhaled lead may have a disproportionately toxic effect compared with its small proportion of lead uptake.

Impaired motor co-ordination has been observed in rats with blood lead levels as low as 35 µg/dL, although no effects were noted at higher concentrations using different measures of co-ordination and reflexes (Zenick et al., 1979; Grant et al., 1980). These abnormalities may be related to cerebellar control of posture and movement. Small effects in children seem to be well documented between 30 and 60 µg/dL; there are a few conflicting reports at levels as low as 25 μg/dL.

There is a large and controversial literature on lead-induced hyperactivity in both children and laboratory animals. The condition is very complex, involving genetic influences, psychosocial factors and many others. David et al. (1983), however, found that chelation-induced reductions in the blood lead levels of hyperkinetic children from 29.3 to 19.5 μg/dL were associated with symptomatic and behavioural improvements. Nevertheless, despite some tempting hypotheses, there is very little that is definitive in the literature. Work with distractable children or those with problems such as inattention has been more rewarding. This has been described at some length by Needleman (p. 225). Needleman and others in the United States and Winneke in Germany have essentially found neurobehavioural deficits to be associated with blood lead levels above 30 μg/dL and possibly somewhat lower in the case of inattention (15-20 μg/dL); the work at low-level exposures (<20 μg/dL) is not supported by more recent results obtained in Britain (see below).

The interest in behavioural effects of lead has been complemented by the development of an extensive literature on lead's potential effects on cognitive development. The earlier work in this field sparked a great deal of controversy, in large measure because the dose-response relationships at low lead exposures became less discernible than other factors including genetic and social ones. Needleman and co-workers (Needleman et al., 1979, 1982, 1985) have made major efforts to overcome these difficulties. Recognizing total body burden of lead to be more significant than the recent exposure measure denoted by blood lead level, they used volunteered deciduous teeth to determine lead levels and found correlations between high lead burdens and low IQ. There were, nonetheless, a number of methodological problems, in that the teeth were volunteered, not randomly sampled, and the analysis, by its nature a one-time event, represented total lifetime burden and could not show any time-related variations. Needleman and his co-workers were also able to analyse umbilical cord blood lead, and to follow children's behavioural characteristics in a structured way using carefully devised questionnaires (Rabinowitz and Needleman, 1982; Rabinowitz et al., 1984). There is little doubt that lead is implicated in neurobehavioural problems and cognitive deficits in children at blood lead levels above 30 µg/dL; there is also some evidence of effects at lower levels (Needleman, p. 225; and Bornschein, p. 255).

It was early realized that cross-sectional and retrospective studies could not resolve the epidemiological problems inherent in the neurobehavioural and neuropsychological work, and that the approach should be through prospective longitudinal studies, recognizing that they will take several years to complete. Currently five of these studies are under way, based in Boston, Cincinnati, Cleveland, Glasgow and Port Pirie (Australia). Preliminary results from the longitudinal studies indicate that foetal exposure may affect birth weight and very early performance measures. Dietrich (p. 269) presents a detailed report on the progress of the Cincinnati study.

Confirmation of dose-related lead-induced learning and behavioural problems comes from the longitudinal experiments of Rice and her co-workers (p. 247) with monkeys dosed from birth, some of which are now 10 years old. They have demonstrated the same types of impairment at blood lead levels of 15 µg/dL that have been reported by others in children. Rice (1985) acknowledged that a high dietary lead intake was required to maintain the animals at this level, so that the results cannot be directly extrapolated to humans.

An important review by Harvey (1984) showed a striking consistency in the psychometric and behavioural studies made by several authors assessing more than 1200 British children (Smith et al., 1983; Yule and Lansdown, 1983; Yule et al., 1983, 1984; Harvey et al., 1984; Yule and Rutter, 1985). These studies generally support the position taken by the British Medical Research Council (1984) that, once allowance is made for social factors, there is no significant relationship between low body burden of lead and behavioural and cognitive performance. Smith (1985) maintained that:

> if there are any functional effects of lead on IQ, learning or behaviour at these low levels, then they are small, and it may not be possible to detect them with any certainty, amid the much larger 'noise' of social influences. While it is possible that the residual differences which remain between lead groups are due to lead, it is also possible that they are due to social factors not measured, or at least not controlled, in the data.

Barltrop (1985) went even further, asserting that the linkage of lead and brain damage is an "entrenched public belief, sustained by the lay and public press", but that "the basis for some costly environmental lead abatement programs might reasonably be reviewed." It is important, however, to note that the blood lead levels covered by these workers were generally about 13-15 g/dL, so that the data are not directly comparable with much of the US work, where the blood lead levels were substantially higher. Odenbro et al. (1983), for example, found 137 out of 318 pre-school children to have blood lead levels between 30 and 60 µg/dL. They observed that perceptual visual-motor ability decreased significantly over the range 12-60 µg/dL, and noted verbal and productivity perceptual visual-motor deficiencies at levels above 29 µg/dL.

Winder and Carmichael (1985) reviewed the ways in which lead has been administered to rats, which have been extensively used in neuropathological and behavioural studies over the last 20 years. Like Weiss (p. 241), who singles out the absence of dose measures and lack of variation, they were sharply critical of the 'bewildering' number of doses administered. Winder and Carmichael suggested that inadequate characterization of dose regimens has impaired understanding of any effects and their correlation to human exposure, which is at best tenuous, and that many of the model systems do not address the problems of human clinical or subclinical intoxication. In their review they accept the more recent work on the sequestering of lead into selective areas of the central nervous system of rats, particularly the forebrain (and hippocampus) and the cerebral cortex at a blood lead level as low as 13.8 µg/dL (Collins et al., 1982). Prolonged exposure of developing rats to this level was found to affect circadian spontaneous locomotor activity (Collins et al., 1984). Although this cannot be directly extrapolated to humans, Weiss (p. 241) asserts that the evidence of the animal work is too compelling to be ignored. Discussing experiments with laboratory animals and their implication for assessing human lead hazards, he finds the most cogent evidence to come from behavioural toxicology. Weiss believes that experiments involving schedule-controlled behaviour can test the animals' abilities to make choices in ways analogous to survival-dependent foraging decisions in the wild.

Recent publications by Harlan et al. (1985) and Pirkle et al. (1985) shift the centre of interest to adults. They have used NHANES II data to identify a positive correlation between blood lead levels and both systolic and diastolic blood pressure in white American males, aged 40-59. This impressive project is described by Schwartz (p. 379). This age group was chosen so that data from the United States Pooling Project and the Framingham study could be used to estimate the number of cardiovascular episodes and deaths from myocardial infarctions and strokes that would be averted by the elimination of lead from gasoline. Based on the decrease of mean blood lead level from 16.8 to 11.8 µg/dL between 1976 and 1980, they estimated that the incidence of clinical hypertension would decrease by 17.5%, myocardial infarctions by 4.7%, stroke by 6.7% and death from all causes by 5.5% (EPA, 1985).

Shaper and Pocock (1985) point out that hemoglobin, serum albumin, dietary vitamin C, potassium, riboflavin and oleic acid are all independently related to either systolic or diastolic blood pressure at a statistical significance equal to or greater than that shown for blood lead levels. Nevertheless, there is an increasing body of evidence that points to, at best, a weak association between blood lead level and blood pressure, and a recent analysis by Neri and Hewitt (1986) showed the 1978-79 Canada Health Survey data to be both consistent with the prevalence of mild hypertension noted in the British Regional Heart Study (Shaper et al., 1981) and qualitatively consistent with the NHANES II regression analysis.

It is fair to say, however, that controversy remains as to the validity of using the NHANES II blood pressure and blood lead data together with the Pooling and Framingham information to predict the incidence of lead-induced cardiovascular events. Shaper and Pocock (1985) claimed that the approach is simplistic. They saw the determinants of hypertension and the factors involved in ischaemic heart disease and atherosclerosis as being complex, and felt that it is precipitate to claim an immediate effect of blood lead on cardiovascular mortality. This view was shared by the US EPA Clean Air Science Advisory Committee in April 1985 (CASAC, 1985).

Lead interferes with biochemical processes such as heme synthesis and oxidative phosphorylation in kidney mitochondria at blood lead levels as low as 15-20 µg/dL, but renal function is impaired only at substantially higher levels. Temporary decreases in tubular reabsorption (which may be related to biochemical energy metabolism) have been observed at 40 µg/dL and possibly slightly lower levels. Irreversible kidney damage has been noted only in adults exposed for long periods at blood lead levels in excess of 70 µg/dL; there is little reliable information on chronic renal dysfunction in children.

The placenta confers little protection from lead on the foetus. Barltrop (1969) reported placental transfer and continued accumulation of lead from the 12th week of pregnancy. Umbilical cord, maternal and infant blood lead levels are strongly correlated and do not vary significantly (Clark, 1977; Angell and Lavery, 1982). ALAD is negatively correlated with blood lead levels in the mother and newborn infant (Lauwerys et al., 1978). Delays in the development of exploratory and locomotor behaviour in neonate male rats have been shown to result from pre-natal exposure of the mothers at an average blood lead level of 38 µg/dL in carefully designed experiments (Crofton et al., 1980). Other effects on post-natal physical and behavioural development have also been reported (Grant et al., 1980, Needleman et al., 1984).

It would thus appear reasonable to presume that the demonstrated effects of lead on the hematopoietic system at levels below 20-25 µg/dL could be transmitted to the developing foetus and effect its early development. Indeed, Beattie et al. (1975) showed that women exposed to somewhat higher levels of lead in drinking water (800 ppm) had a higher percentage of retarded offspring. Anomalies of various types have been noted in animals, but most cannot realistically be extrapolated to humans, so that subtoxic effects on the development of the central nervous system are difficult to assess (Winder and Carmichael, 1985). Needleman and his co-workers (1984) suggested that increases in benign tumours and skin conditions might be ascribed to an interaction between lead and other teratogenic factors, as they were not able to find a statistically significant association with cord blood lead levels.

Schwartz (p. 151) describes the study on the relationship of gasoline lead to blood lead done by the US Environmental Protection Agency. Several data bases were used, including the NHANES II study, and the statistical results indicated a highly significant regression coefficient, consistent across all the data sets. The US EPA believed the association to be causal because dietary and other factors such as paint lead did not appear to account for the changes associated with gasoline lead; the results suggested that "more than one half of the lead in the average American's blood in the second half of the 1970's was due to gasoline". Despite a very thorough statistical analysis and treatment of confounding variables, this work has been widely criticized. Elwood (p. 123), for example, stresses that the significance of the various sources of lead varies with locality, and that strict conformance with epidemiological requirements is required for proof of causality. Bradley (p. 415) maintains that the NHANES II data base was not designed for use in this way nor is it appropriate because it contains time-associated biases.

There is no doubt that gasoline lead, whether inhaled or ingested with food or dust, is a significant source of lead, but the contribution that it makes to uptake is unquestionably site-dependent, as shown by the Isotopic Lead Experiment in Italy (Facchetti and Geiss, 1982; Colombo and Fantechi, 1983; Facchetti, 1985) and the regional data assembled for Britain by the Royal Commission on Environmental Pollution (1983). It has also been observed that blood lead levels have decreased over the same time period in many other industrial countries, despite the fact that there has been little or no change in the lead content of their gasoline. Where exposures are high, especially in the case of children, the primary causes of lead exposure are likely to be found elsewhere--in soils, dusts, food, water or paint. In this context, Dabeka (p. 181) considers that the average infant in Canada consumes substantially more lead from food on an absorption-adjusted basis than the FAO/WHO provisional tolerable daily intake for adults (11.5 as against 7.1 μg/kg/day).

Harvey (1984) raised the question of why children raised in similar environments may have different lead burdens. He cited Heard and Chamberlain's (1982) suggestion that dietary factors may influence the body's handling of lead, that diet and dust may be directly responsible for lead uptake (Bander et al., 1983; Ryu et al., 1983) or that other aspects of child care need to be considered as predictors of lead exposure and cognitive development (Milar et al., 1980; Hunt et al., 1982). Harvey felt that the lesson from the work in Britain is the need to lessen exposure to lead and, like Elwood (p. 123), believed that attention to sources is essential to prevent lead burdens from rising.

It is relatively easy to identify the sources of lead to which populations at large may be exposed, but it is far more difficult to assess the significance of the individual sources, because many factors drastically affect the contributions to total exposure both regionally and nationally (Elwood and Gallacher, 1984). A case in point is the Isotopic Lead Experiment in the Turin area of Italy, which showed gasoline to contribute up to 26% of lead in blood, very different from Schwartz's calculation of 50% for the United States (p. 151). The British Royal Commission on Environmental Pollution (1983) reported wide regional variations in the United Kingdom that could not be explained solely by population density or industrial activity. It also noted lower values than expected in several large towns. Awareness of such differences is particularly important in Canada, where the similarities with the United States are stressed to the exclusion of the very real differences that exist. These extend to the political and other institutions established to resolve environmental and other problems, and the ways in which they operate in response to fundamentally different social and economic concepts and priorities.

Legislation is initiated by individual legislators in the United States and consequently quite minutely mandates the regulatory actions to be taken by the Administration. The requirement to maintain a parliamentary majority to be able to govern in Canada means that all legislation must have support of the government, so that it tends to be enabling in style, allowing the ministers responsible to make regulations that are consistent with the Act. Thus the processes for assessing and managing toxic materials differ markedly in the two countries.

Grant (p. 467) describes the regulation of airborne lead in the United States, which involves the establishment and enforcement of a National Ambient Air Quality Standard for lead, and the phase-down of the use of lead in gasoline, which was the largest and certainly the most widely dispersed source of lead. The Air Quality Standard is based on a process that involves publication of a criteria document, a most impressive and thorough review of the state of the scientific and medical knowledge of the behaviour of lead and its effects on populations, and it is periodically reviewed and revised. Regulations to ensure compliance are proposed by the Administrator of the US EPA and are then subject to a public review process. The process also involves a cost-benefit analysis and other societal value judgements of the impact of regulations.

Nriagu (p. 61) notes the ubiquity of lead in Canada, and reviews the sources of lead contamination of its atmosphere, soil and water. It is quite clear that Canada's very real and most significant lead problems are not the same as those of the United States. They arise in different ways and they will need different solutions. There are indeed problems with 'hot spots', but paint lead from deteriorated housing in decayed urban cores is not a significant one; the urban 'hot spots' arise largely from smelter and other lead-working operations which have resulted in soil contamination over the years. Nor does toxicity requiring chelation treatment seem to occur to any extent; the cases reported from major pediatric hospitals in older urban centres in recent years are few in number, in both comparative and absolute terms, and seem to have arisen from easily explained accidental exposures (RSC, 1986). The selection of the policy options that are appropriate to the needs of a country or region is far more important than costly and unnecessary approaches induced by uninformed demand for action, based on very real fear and frustration at the ill-explained multiplicity of environmental toxins that are so widely reported. Such demands can only divert increasingly scarce resources away from where they should be spent.

Exercises in the development of social policy inevitably result from value judgements that combine soundly based scientific knowledge relating to sources, pathways and health effects with social and economic perceptions into a politically acceptable set of approaches. This is not an easy task and, as Elwood and Gallacher (1984) pointed out, the roles of the actors involved are often confused by multiple loyalties; for example, the objectivity of scientists may be distorted outside their spheres of expertise by their views as citizens in their relations with the media, thereby prejudicing the contribution that science can make to developing effective social policy. Unlike Elwood and Gallacher, Grant (p. 467) believes that investigatory bodies have to confront both the scientific and socio-political realities, and he provides an elegant description of the way in which the scientific concerns were handled in the US policy process.

Clearly, in responding to the public health concerns posed by issues such as environmental lead, each country or jurisdiction needs to understand the broad perspective presented by the knowledge base contributed by worldwide research. Equally important, however, is the ability to identify its own problems and use the available information on which to base judgements of individual needs and priorities so as to develop appropriate specific responses.

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2. MEASUREMENT OF LEAD

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Selection of Exposure Index

There are two general approaches to evaluating the level of lead in the body. The first involves measurement of the concentration of lead in a body fluid (blood, urine) or in a tissue (teeth, bone). The alternative approach is to measure the concentration of a heme precursor in blood (protoporphyrin IX) or in urine (δ-aminolaevulinic acid (ALA); coproporphyrin) or to measure inhibition of ALA dehydratase (ALAD) in blood. It is generally accepted that, among the various measurements of lead itself, the concentration of lead in the blood is the most useful. Lead in urine shows much greater day-to-day fluctuation, and lead in teeth or bones has two serious limitations: (i) one-time only analysis in the case of shed deciduous teeth, and (ii) expense and inadequate characterization of methods in the case of lead in bones or teeth *in situ*. For these and other reasons to be considered below, the concentration of lead in blood is by far the most popular and useful of the direct measurements of lead.

The alternative of measuring heme precursors or ALAD inhibition has been recommended by some because sample contamination with lead is not a problem. Moreover, it is at least possible that these measurements more accurately reflect the biologically active fraction of circulating lead and may therefore be more relevant to the purpose of lead measurement to assess potential risk of harmful effects.

There are very few studies which have compared the fidelity with which the various indices of lead exposure correlate with degree or frequency of health effects. Hammond et al. (1980) compared blood lead (PbB), free erythrocyte protoporphyrin (FEP), ALA in urine (ALAU) and ALA in plasma (ALAP). Correlations of these measures with indices of health effects (hemoglobin (Hb), serum creatinine (SCr) and frequency of symptoms) were determined in a group of smelter workers. The results suggest that PbB, ALAU and ALAP are all superior to FEP, except possibly in regard to effects on hematopoiesis (Table 1).

Table 1.

Correlation of indices of exposure with effects (Hammond et al., 1980).

	Effect					
	Hb		SCr		Symptoms	
Exposure Index*	r^2	p	r^2	p	r^2	p
PbB	0.23	0.03	0.37	0.003	0.16	0.03
FEP	0.21	0.04	0.13	0.13	0.10	0.10
ALAU	0.27	0.02	0.26	0.02	0.19	0.02
ALAP	-	-	-	-	0.17	0.03

* Analytical coefficient of variation (%): PbB = ±3.4-4.4; FEP = ±1.3-1.8; ALAU = ±4; ALAP = ±3-14.

One other study is in general agreement with this conclusions at least in regard to PbB versus FEP (Spivey et al., 1979), whereas others report that FEP correlates better with health effects than with PbB (Lilis et al., 1977). All three of these studies involved heavily exposed workers. In all three cases many of the subjects had PbB levels in excess of 60 µg/dL. If one were to attempt to relate these indices to effects at lower PbB levels, correlations for heme precursors versus effect would be more difficult to perceive or might be lost altogether, because these precursors have a high and variable background level independent of lead exposure. This is clearly evident when the relationship of ALAU or FEP to PbB is analysed. Thus, in the case of ALAU, a relationship to PbB is evident only when PbB exceeds 40 µg/dL (Figure 1; NAS, 1972). Similarly, the apparent threshold for an interaction between FEP and PbB is not discernible when PbB is below approximately 15 µg/dL (Figure 2; Piomelli et al., 1982; Hammond et al., 1985). Thus, the sensitivities of ALAU and FEP as indices of exposure are of limited utility in the range of lead exposure likely to occur in the general population. As a matter of fact, the new guidelines for lead screening in children being published by the US Centers for Disease Control conclude that FEP as a screening device is sensitive only to PbB levels as low as 25 µg/dL. If one were to screen for elevated PbB using FEP, the imprecisions would result in two problems, false positives and false negatives. Assume, for example, that one is using FEP greater than or equal to 35 µg/dL to detect PbB greater than or equal to 25 µg/dL. In a certain percentage of cases PbB levels will actually be found to be less than 25 µg/dL (false positives), and in a certain percentage of cases with FEP less than 35 µg/dL PbB would have been greater than or equal to 25 µg/dL. The main concern is in regard to false negatives. Because we have been determining FEP and PbB on all subjects at all ages, the issue of false negatives could be examined. It may be noted from Figure 3 that 19% of children with FEP less than 35 µg/dL proved to have PbB levels greater than 25 µg/dL (false negatives).

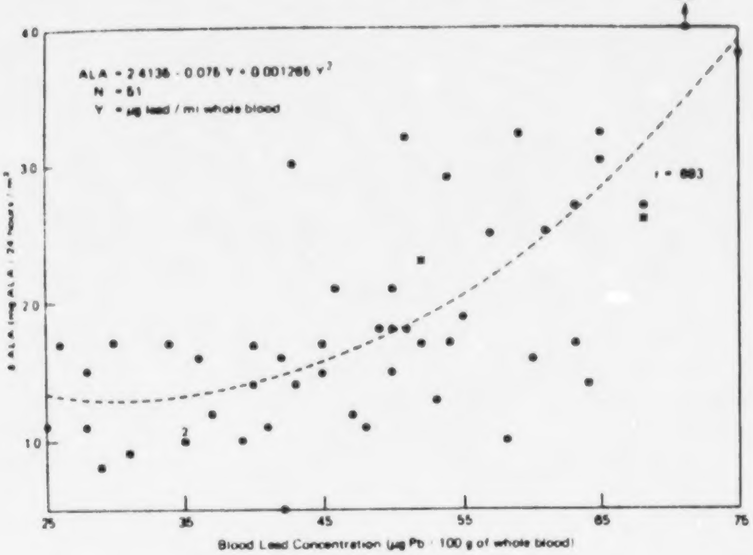

Figure 1. Relation between blood lead concentration and daily excretion of ALA in urine in a group of young children without clinically evident lead poisoning.

Note: The group consisted of 51 children between 1 and 5 years of age drawn from an inner-city clinic population in Baltimore, MD. The range of blood lead concentration was 25-75 µg/100 g of whole blood. Whole blood samples for lead determination were drawn on admission to the hospital and analysed by the laboratory of the Baltimore City Health Department by a dithiozone technique. ALA output was measured in quantitatively collected 24-h urine specimens by a method that excludes aminoacetone. Statistical analysis of the data indicates that ALA output is related to age and height but that it is best related to surface area in young children, in that the slope and regression between daily ALA output and surface area intersect at the origin. Therefore, expression of ALA output as mg/m^2 per 24 h completely compensates for differences among the children due to age and body mass. A highly significant curvilinear relation is best fitted by the following quadratic equation: mg/m^2 per 24 h = 2.4135 - 0.07500 (blood lead) + 0.001265 $(\text{blood lead})^2$. For this fitted quadratic equation, $p < 0.01$, and the standard error for the fitted line is ±0.6. A highly significant linear relation is also found in this group between blood lead concentration and the log of ALA excretion ($p<0.001$). Within this narrow range of blood lead concentration (25-75 µg/100 g of whole blood), the data suggest that ALA excretion apparently increases only as blood lead concentration rises above approximately 40 µg/100 g of whole blood; however, the absence of a threshold for this relation cannot be excluded in these young children. Statistical analyses were performed by Dr. David F. Mellits, Department of Pediatrics, The Johns Hopkins University School of Medicine. These unpublished studies (J.J. Chisolm, Jr., personal communication) were supported by DHEW grant EC-ROI-00201 from NIH, NSMHA study project 464, MCHS grant MC-R-240012-01-0, institutional research grant FR-53-78 to The Johns Hopkins University School of Medicine, and a grant from the Thomas Wilson Fund, Baltimore, MD. The studies were carried out in the Pediatric Clinical Research Unit of The Johns Hopkins University School of Medicine, which is supported by DHEW grant R-MOI-00052 (NAS, 1972).

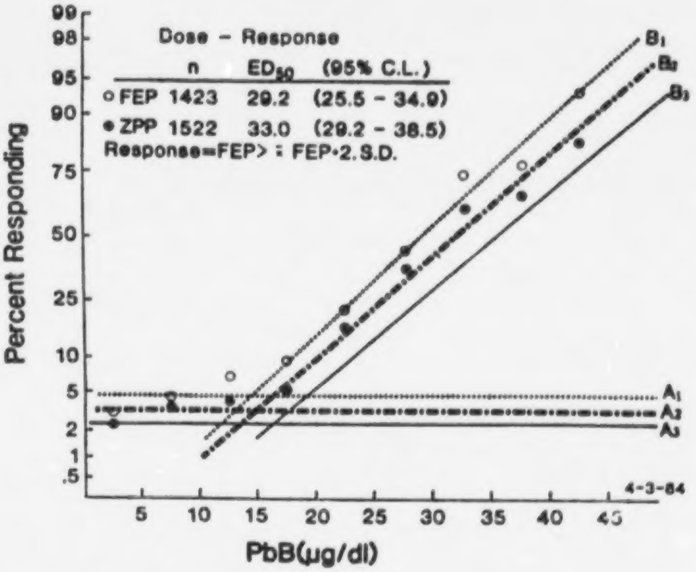

FIGURE 2. DOSE-RESPONSE RELATIONSHIPS DEPICTING PERCENT OF THE COHORT AT ANY GIVEN PbB LEVEL WHICH EXHIBITED A ZPP OR FEP VALUE TWO STANDARD DEVIATIONS OR MORE ABOVE THE COHORT MEAN FOR EACH AGE GROUP.

A_1 = BACKGROUND FEP + 2 S.D., THIS STUDY

A_2 = BACKGROUND ZPP + 2 S.D., THIS STUDY

A_3 = BACKGROUND FEP + 2 S.D. (PIOMELLI *ET AL.*, 1982)

B_1 = DOSE-RESPONSE, FEP, THIS STUDY

B_2 = DOSE-RESPONSE, ZPP, THIS STUDY

B_3 = DOSE-RESPONSE, FEP (PIOMELLI *ET AL.*, 1982)

Data are from ES-01566.

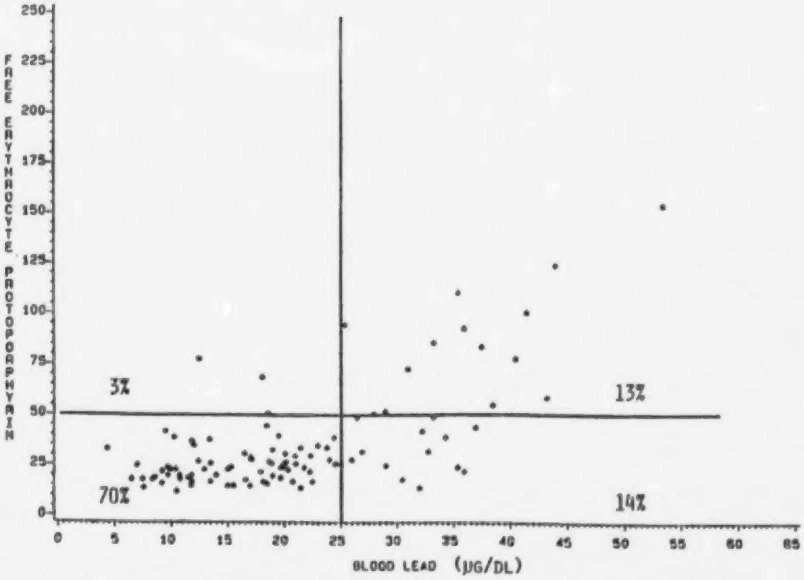

Figure 3. The relationship between FEP and PbB in 24 month-old children, n = 100 lower right quadrant = false negatives (FEP $\leq$ 50, PbB > 25) upper left quadrant = false positives (FEP $\geq$ 50, PbB $\leq$ 25). Data are from ES-01566.

In summary, heme precursors are poor indicators of low-level lead exposure because of high and variable background levels unrelated to the presence of lead.

Accuracy and Precision of Blood Lead Measurement

Accuracy and precision will vary in accordance with the analytical method used and with the skills of the analyst. In the United States the two most commonly used analytical approaches are atomic absorption (AA) spectrophotometry and anode stripping voltammetry (ASV). Both types of instrumental procedures as used today are quite sensitive, even for the detection of PbB in the range commonly encountered in the general population. Numerous variations exist in the specific instrumental and procedural details used. Thus, atomic absorption and anode stripping methods vary considerably as to the ashing procedure which precedes actual spectrophotometric measurement. Some methods require wet oxidation of the sample prior to analysis whereas others do not. Only one study of which we are aware has attempted to compare the analytical accuracy and precision of these two general methods (Boone et al., 1979). In order to assess the performance of the method it is necessary to know true values. 'Truth' is probably best determined by isotope dilution mass spectrometry (IDMS). Boone et al. (1979) established 'true' PbB by IDMS for a number of blood samples which had been submitted to a large number of laboratories for analysis by five general atomic absorption methods and by anode stripping voltammetry. Accuracy and precision were compared. The results are summarized in Table 2. Two things are evident from this table: (i) precision improves using either AA or ASV as PbB increases, and (ii) ASV is superior to AA with regard to precision. In addition, ASV was found to be superior to AA methods with respect to accuracy (data not shown).

Table 2.

Summary of lead method performance (Boone et al., 1979).

μg/dL Pb, IDMS	Coefficients of Variation (%) 5 AA Methods Range	Mean	ASV
12.4	41-135	81	39
13.0	50-136	45	19
15.9	36-84	39	63
22.2	23-50	33	14
27.3	2-24	18	19
53.8	4.28	17	9
68.4	10-28	18	17

Problems Using ASV

Our own experiences in measuring PbB have been limited to the use of one instrument, Model 3010A, ESA, Burlington, MA. The use of this instrument entails the mixing of 100 μL whole blood with 2.9 mL of a solution which serves to allow Pb to migrate freely to a test electrode using a negative potential. By reversing the current to an anodic potential, the metals are stripped off sequentially. The current resulting from the migration of the metals yields a sequence of peaks whose magnitudes are a function of metal concentration. Recommended use entails calibration with only two lead standards (< 5 and >90 μg/dL, respectively). Lead concentration is estimated using an internal integrator of area under the lead peak. Results are then displayed on a digital readout. This technique has proved totally unsatisfactory in our hands. The integrator system led to underestimation of low lead values and overestimation of high lead values. Moreover, the integrator system approach invalidated results in which high levels of copper in serum occurred (pregnant women), as the copper peak in such cases encroached on the lead peak, resulting in spuriously low lead concentrations. These problems have been resolved by calculating lead concentration from peak height. The instrument is calibrated using blood analysed by IDMS.

We also participate regularly in two proficiency testing programmes: Centers for Disease Control (CDC) and State of Pennsylvania. 'Truth' in both cases is established by consensus among reference laboratories (CDC) and all participating laboratories (Pennsylvania). None of these laboratories (unfortunately) utilizes IDMS. Correspondence of our results to those from these two proficiency programmes is summarized in Table 3. It is clear that calibration of our ASV system using IDMS calibration with peak height measure-

Table 3.

3010 A ASV performance in CDC and Pennsylvania PbB proficiency programmes.

Calibration with ESA Stds. and using the digital readout:	Calibration with IDMS Stds. and using peak height measurements:
CDC	CDC
$N = 128$	$N = 39$
$R = 0.975$	$R = 0.994$
$Y = -2.33 + 1.12$ (CDC ref. $\bar{X}$)	$Y = -0.485 + 1.04$ (CDC Ref. $\bar{X}$)
Pennsylvania	Pennsylvania
$N = 60$	$N = 20$
$R = 0.979$	$R = 0.993$
$Y = -4.99 + 1.10$ (Pa. ref. $\bar{X}$)	$Y = 2.85 + 0.97$ (Pa. ref. $\bar{X}$)

ments has materially improved concordance with respect to both accuracy and precision. The great similarity in slope and intercept values for our results (using IDMS calibration) and theirs also suggests that the two proficiency programmes correspond rather closely to each other.

Sample Storage

In our prospective study of the health effects of lead in children, PbB is measured at least once every 3 months. It is extremely important to check frequently for potential problems which might compromise precision and accuracy. Several steps are taken to avoid such problems. With lead concentration confirmed by IDMS, day-to-day accuracy and repeatability can be monitored as well as reproducibility and drift over time. One particular pool of adult blood has been drawn from repeatedly for this and other purposes. It was found to contain lead at 10 µg/dL by IDMS. Subsamples have been stored at -15 to -25°C in 5-mL Fisher brand polystyrene culture tubes. Over a period of 9 months, 26 samples have been analysed in duplicate. The mean of duplicates was 11 µg/dL, with a coefficient of variation of 8%. There was no significant upward or downward drift over that period (Figure 4).

Temporal Trends in Blood Lead Levels

It has long been observed that the incidence of elevated PbB in children is higher in the summer than in other seasons. It has also recently been reported that, even in the absence of excessive lead exposure, young children have higher PbB levels than older children (Mahaffey et al., 1982). Our current prospective study has allowed us to characterize temporal trends in some detail.

The first temporal trend we have noted is that PbB levels tend to rise substantially in the first year of life, even among children whose PbB

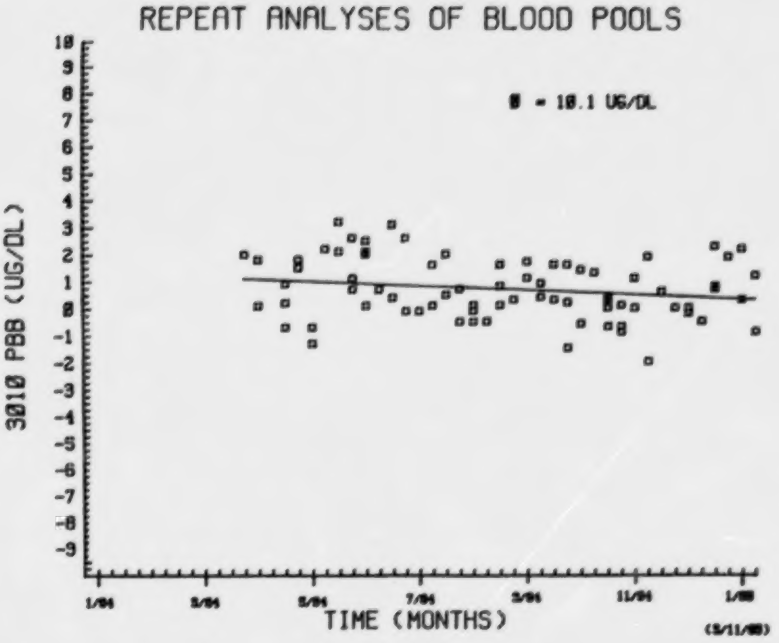

Figure 4. Effect of blood storage on PbB. The original PbB determination by ID-MS was 10.1 µg/dl. The ordinate scale represents PbB deviations from 10.1 µg/dl in µg/dl. The fitted regression line does not deviate significantly from zero slope. Data are from ES-01566.

levels never rise above 15 µg/dL (Figure 5). There also is a strong seasonal trend, in which PbB levels among children with even only very moderate lead exposure exhibit a pronounced circum-annual PbB rhythm, with peaks occurring in the early fall and troughs in the late winter. This rhythm is most readily observable in children whose lead exposure is relatively low and stable, i.e. in situations where the rhythm does not become obscured by moves from low to high exposure situations or vice versa. This rhythmicity is evident even during the first few months of life. Figure 6 depicts data for a pair of twins from birth through 45 months. Peak-to-trough PbB levels may vary by 50% or more. Awareness of the existence of this rhythm aids in the interpretation of PbB. Thus, for example, a PbB level determined in February or March is likely to increase substantially in the succeeding several months, and one determined in August probably exaggerates the average PbB level of the child.

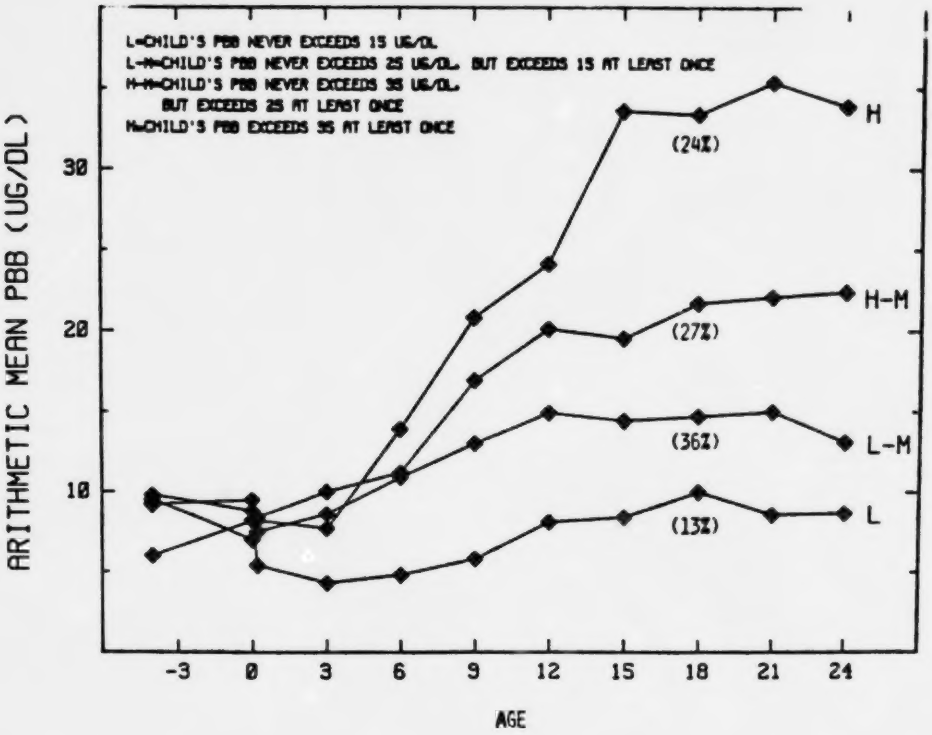

Figure 5. Developmental profile of PbB in children categorized according to peak PbB. Data are from ES-01566.

In spite of these and other influences on PbB level, such as change in residence with consequent change in the level of lead exposure, any given PbB determination in a child is still highly correlated with past PbB level and, therefore, reflects fairly well the level of lead burden over recent time. This strong relationship between past and current PbB level is depicted graphically in Figure 7. At 12 months of age and beyond, any given PbB level is highly correlated with PbB levels during the previous 6 months. Correlations with earlier PbB levels (e.g. 12 months before) do not attain the same level until later in the child's life. Nonetheless, an accurately determined PbB level in a child, determined during the period of generally maximal PbB level (18-24 months), provides a reliable index of the child's recent lead exposure.

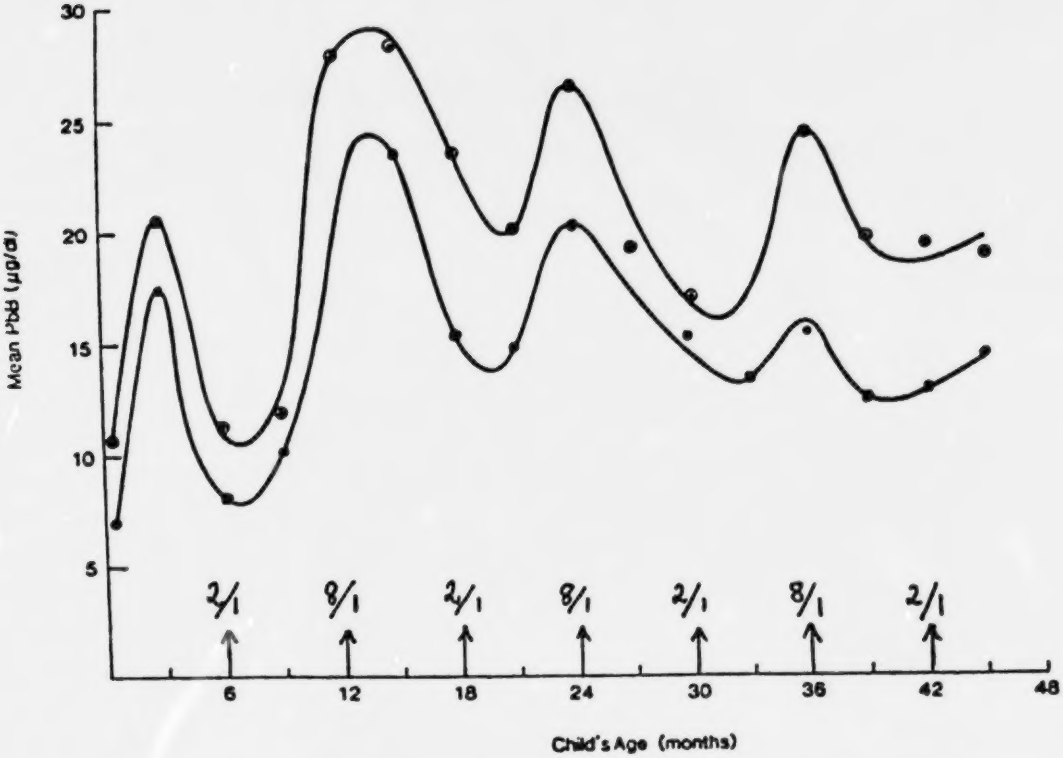

Figure 6. Individual PbB profiles for a pair of black, male infant twins residing in rehabilitated housing for four years. Each data point is the average of duplicate determinations on a single venous sample. Note the strong seasonal variation in PbB concentration. Children were born 8/1/80. Data are from ES-01566.

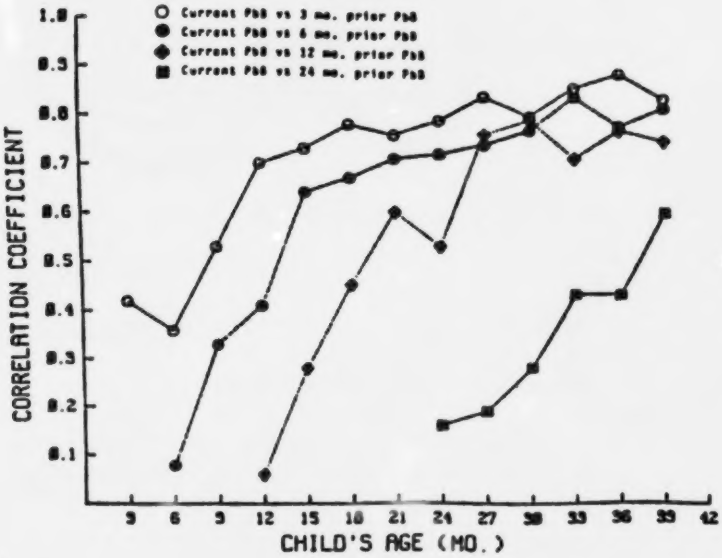

Figure 7. Correlograph depicting the changing strength of PbB correlations as the child develops. Data are from ES-01566.

Acknowledgements

All original data cited were obtained with support of a grant from the National Institute of Environmental Health Sciences, ES-01566. Although the original data are presented by P.B. Hammond, they represent the collective efforts of a large staff of investigators, notably R.L. Bornschein, S.B. Roda and P. Succop.

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3. METHODOLOGICAL ASPECTS OF GRAPHITE FURNACE ATOMIC ABSORPTION SPECTROPHOTOMETRY IN BLOOD LEAD ANALYSIS

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Introduction

Flame atomic absorption spectrophotometry (AAS) is regarded as the technique of choice for many forms of trace element analysis (Tsalev and Zaprianov, 1983). However, the inherent low efficiency of flame atomization results in lower detection sensitivity relative to other trace metal analysis techniques. In 1961, L'vov suggested a method for the quantitative determination of many elements, using the absorption spectra generated by atoms that were vaporized in a graphite cuvette. Massman (1968) applied this principle to the development of a graphite furnace. Modern graphite furnace atomic absorption spectrophotometry (GFAAS) methods have detection sensitivity values which approach the parts per trillion (ppt) range and sensitivities commonly within the parts per billion (ppb) to parts per million (ppm) range.

Although a large number of analytical methods are currently available for the determination of lead in blood, GFAAS is one of the most important of these techniques given its high sensitivity, small-size sample requirements and the possibility of direct sampling. Nevertheless, it has some serious drawbacks and limitations: background and other interference problems, carbide formation, relatively complicated calibration, electronic problems associated with measuring fast transient signals, optical problems associated with the critical need for optical alignment, and a high contamination risk.

Before 1978, only a limited number of simple and direct GFAAS procedures had been published. In 1977, L'vov et al. proposed inserting a graphite platform into Massman-type furnaces to decrease the interference effect. To decrease the effect of background absorption, continuum source (high-intensity ultraviolet) and Zeeman effect optical mechanisms have been used. Detailed investigations and reviews indicate that the following combination of operating parameters is a major advance for the analysis of lead in blood (Tsalev and Zaprianov, 1983): (i) L'vov platform, (ii) gas stop conditions during atomization, (iii) peak area and peak height detection facilities, (iv) spectrometer with high-speed response electronics, and (v) efficient background correction.

The above-stated parameters are part of the stabilized temperature platform furnace (STPF) concept which was first introduced in 1981 (Slavin et al., 1981). Although this concept is a major advance of GFAAS instrumentation for blood lead analysis, practical methodological aspects of this analysis have received little attention.

This report involves the comparison of two blood lead analysis methodologies and provides the opportunity to illustrate some potential pitfalls which can be encountered in the analysis of lead in blood by GFAAS. The original blood lead analysis programme generated values that were statistically different from the values obtained from identical samples analysed by independent laboratories involved in interlaboratory blood lead analysis programmes. Modification of the original programme was necessary to obtain blood lead values which were comparable with those of independent interlaboratory programmes.

Background

GFAAS is based on the detection of absorption of light radiation by free atoms which are thermally excited in a heated graphite furnace (tube or cup cuvette). A small sample aliquot (1-70 µL or 0.1 to a few milligrams) is introduced into the furnace, which is optimally aligned in a spectrophotometer light path and is enclosed in an inert gas (nitrogen or argon) atmosphere. The graphite furnace is electrothermally heated in accordance with a temperature programme to remove the sample solvent, organic matter and/or volatile matrix constituents, specifically volatilize the analyte and eventually expel the sample residues. Given that the sampling and sample preparation procedures are selected properly, an optimized temperature programme should produce an absorption peak signal which can be related to the concentration of analyte in the sample by the Beer-Lambert relation:

$$A = \log {}^{I_o}/_{I} = kC$$

where

A = absorbance signal (peak height or peak area)

I_o = intensity of reference beam

I = intensity of transmitted beam

k = relation constant
C = concentration of analyte

This relation is the mathematical basis for the calculation of the analyte concentration. A typical calibration curve used in this form of analysis is shown in Figure 1.

As with many analytical techniques, and especially with the trace metal analysis in biological materials, precautions must be taken in the sampling and sample storage, sample preparation, calibration and analyte detection

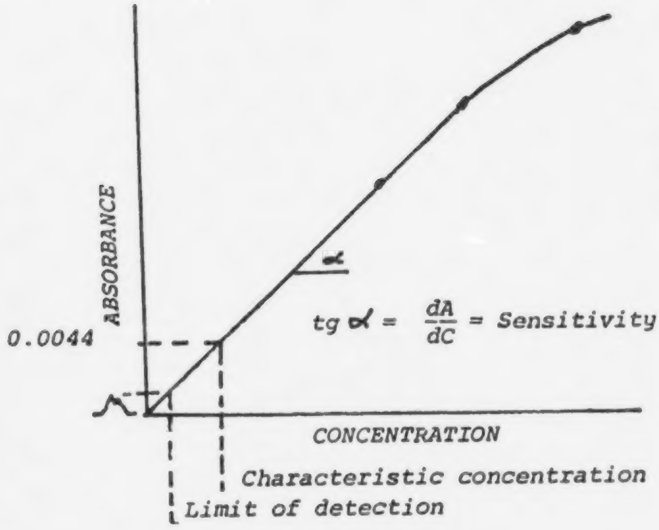

ABSORBANCE
0.0044
$tg\,\alpha = \frac{dA}{dC}$ = Sensitivity
CONCENTRATION
Characteristic concentration
Limit of detection

FIGURE 1. Spectrometry Calibration Curve (general)

stages. These will be addressed to define the major parameters which must be considered in the development of a blood lead analysis programme by GFAAS.

Sampling and Storage

Blood specimens for blood lead analysis are routinely performed by venipuncture. Specimens of capillary blood are easily obtained, but they are problematic given their poor representivity, contamination control and potential dilution by lymph. Contamination control is of the highest importance given that blood lead analyses are commonly performed at the nanogram to milligram per millilitre levels. Extraneous additions of lead have been noted to originate from needles, syringes, collection tubes, rubber stoppers, skin and perspiration, as well as from the sample anticoagulants (heparin, EDTA, etc.) and airborne particles (Subramanian, 1984; Alcock, 1984).

Major contamination sources and their controls are shown in Tables 1 and 2. Common practices of analytical procedure verification are outlined in Table 3.

Table 1.

Major contamination sources (Subramanian, 1984).

Air	- Dust, particulates
Apparatus	- Stainless steel and other metal-containing items (e.g. bench tops, hood linings, ovens)
	- Laboratory ware (glass, plastics, knives, syringes, needles, vacutainers, stoppers, pipette tips, etc.)
Reagents	- All except precious metals
Analyst	- Fingers, hair cosmetics, watches, jewellery, etc.

Attempts have been made to predict the behaviour of lead in blood during storage. Often, although not consistently, the level of lead drops as a result of container wall absorption or volatilization from the container (Williams, 1979; Méranger et al., 1981). For short-term storage, blood lead samples are generally stored at 4°C, whereas for long-term (greater than 3 months) storage, the samples are deep-frozen (-20°C) or lyophilized.

Table 2.

Some simple contamination control measures (Subramanian, 1984).

Measure	Rationale
1. Clean the work area	To avoid obvious contamination
2. Wear talc-free gloves	Sweat and talc are known sources of metals
3. Acid-wash glass and plastic	To prevent leaching and absorption of metals
4. Sealed specimen storage	To avoid contact with ambient air
5. Minimum sample size	To minimize additions and contact with laboratory ware
6. Use high-purity reagents	To reduce addition of contaminants
7. Minimize reagent additions	Same as above
8. Direct, microscale analytical procedures	To avoid excessive handling and transfers; to minimize surface area contact with containers and air

Table 3.

Verification of analytical procedures (Subramanian, 1984).

Measure	Aspect Evaluated
Analysis of SRM*	To identify systematic and random errors
Interlaboratory comparisons	
1. Collaborative survey	Method evaluation
2. Co-operative survey inter-method comparisons	Disclosure of unreliable methods; disclosure of error and assessment of relative variability

* Standard reference materials.

Sample Preparation

Direct analysis (without sample preparation) has been done using 2 µL of undiluted, hemolyzed blood specimens. However, with most graphite furnaces, the difficulties encountered with undiluted or slightly diluted blood samples include (i) strong signal interference by the blood matrix salts, (ii) sensitivity drift, (iii) poor reproducibility, and (iv) the accumulation of non-volatile residues. Recent GFAAS sample preparation procedures favour the dilution (2- and 20-fold) of the sample and/or the use of matrix modifiers instead of the once popular and more time-consuming co-precipitation, derivatization and liquid-liquid extraction, or ashing techniques.

Calibration

Ideally, the calibration matrix and analyte must be identical to the sample to be analysed. Furthermore, the amount of analyte added to or already present in the sample must be known. GFAAS blood lead analysis calibration is indirect given that isotope dilution mass spectrometry (IDMS) is the definitive method of analysis and calibration for blood lead at trace concentrations (method discussed by Hammond, p. 27). Calibration is therefore accomplished by the following alternative methods:

- standard additions of aqueous lead solutions
- commercially available bovine blood standards pre-analysed by IDMS or Neutron Activation Analysis (NAA)
- pre-analysed human blood standards obtained from interlaboratory studies or from IDMS facilities.

Analyte Detection

Optimization of the instrumental parameters is the key ingredient of an effective and efficient blood lead analysis programme. After proper sample preparation is achieved, the separation and detection of the analyte in the sample matrix depend on the selection of proper thermal characteristics of the furnace and the use of optical background correction. A general outline of this essential step is shown in Table 4.

To illustrate the analytical significance of each of the above parameters, this report will outline and compare the results which were obtained from a systematic optimization programme for the clinical analysis of inorganic lead in blood.

Analytical Procedures

Sampling and Storage

All test and calibration blood lead samples were obtained by venipuncture using conventional stainless steel needles and Becton Dickinson 'Vacutainer' brand trace metal-free (BD #6527) blood collection tubes. All samples were stored at 4°C until analysis.

Sample Preparation

Original Procedure. The original sample preparation procedure involved the addition of 1 volume of whole blood to 15 volumes of 2% Triton X100 solution in a pre-washed (10% nitric acid) centrifuge tube and vortexing for about 30 seconds. The mixture is centrifuged and the clear supernatant (hemolysate) is used for the analysis.

Modified Procedure. The modified sample preparation procedure involved the addition of 1 volume of whole blood to 7.5 volumes of 0.5% Triton X100 solution in a pre-washed (10% nitric acid) centrifuge tube and vortexing for about 30 seconds.

Table 4.

Programme optimization and sample matrix reduction.

Dry Stage

Purpose	Desolvation
Recommended temperature	Slightly below total boiling point of sample
Recommended time	1-3 s/μL of sample (longer time for biological samples)

Ash Stage

Purpose	Organic matrix removal
Recommended temperature	400-800°C depending on sample
Recommended time	0-40 s depending on sample
Notes	1) optical background correction may be necessary 2) chemical modification may be necessary

Heating Rate to Atomization Temperature

Purpose	To give highest absorbance at atomization
Recommended time	Dependent on analyte and matrix (e.g. 2000°C/s for Cu)
Note	Plot of absorbance (atomization) versus ramp rate is useful

Atomization Temperature

Purpose	To give highest absorbance at atomization
Recommended temperature	Dependent on analyte and matrix (eg.. 1800°C for Pb in Ca solution; 1900°C for Pb in Fe solution)
Note	Plot of absorbance (atomization) versus atomization temperature is useful

Calibration

Original Procedure. A standard addition calibration procedure was used for the original analysis. Nitric acid was used to stabilize the aqueous lead standard solution, giving 100 µg/mL of lead in 0.5% nitric acid in deionized water. For individual sample analysis, known amounts of the standard solution were added to 4 equal volumes of the blood sample hemolysates. Aliquot volumes of 10 µL from the individual samples and a pooled sample were injected into the graphite furnace using a multi-sample unit.

Modified Procedure. Calibration was accomplished using pre-analysed human blood lead samples from an interlaboratory programme (Centre de Toxicologie du Quebéc). The preanalysed calibration blood lead sample concentrations were 10.0, 66.0 and 84.0 µg%. Five-microlitre aliquots of the prepared (see above) calibration samples were injected using the same multi-sampling apparatus employed in the original programme.

The original and modified procedures for sample preparation and calibration are summarized in Table 5.

Analyte Detection

For both the original and modified procedures, the 283.3-nm lead atomic absorbance wavelength from a hollow cathode lamp was selected over the 217.0-nm line to minimize non-atomic absorption interference. Background correction from a high-intensity deuterium arc lamp was used in both procedures to correct for background interference. Argon was used as the furnace sheathing gas. The absorbance signal from a Varian graphite furnace GFA 95 was detected using a Varian AA875 spectrophotometer in the peak height mode (spectral band pass = 1.0 nm) at the atomization stage.

Table 5.

Sample preparation and calibration comparison.

Parameter	Procedure Original	Modified
Sample matrix	Whole blood	Whole blood
Element	Pb	Pb
Reagent required	2% Triton X100	0.5% Triton X100
Sample dilution	15-fold	7.5-fold
Centrifugation	Yes	No
Calibration	Standard additions	Interlaboratory blood samples
L'vov platform	No	Yes

The temperature programme for the original procedure is as noted in Table 6. A L'vov platform was not used within the pyrolytically coated graphite furnace in the original programme.

The temperature programme for the modified procedure is as noted in Table 7. A L'vov platform was used within the pyrolytically coated graphite furnace in the modified programme.

Results

Figure 2 shows the calibration curves obtained for the original and modified methods respectively. The parallel slopes of the standard addition calibration curves are indicative of the depressive effect of the blood sample matrices.

When the blood lead values obtained with the original programme are compared with those of the modified programme and the interlaboratory programmes, there is an evident difference between values for each corresponding sample pair, as shown in Table 8.

Table 6.

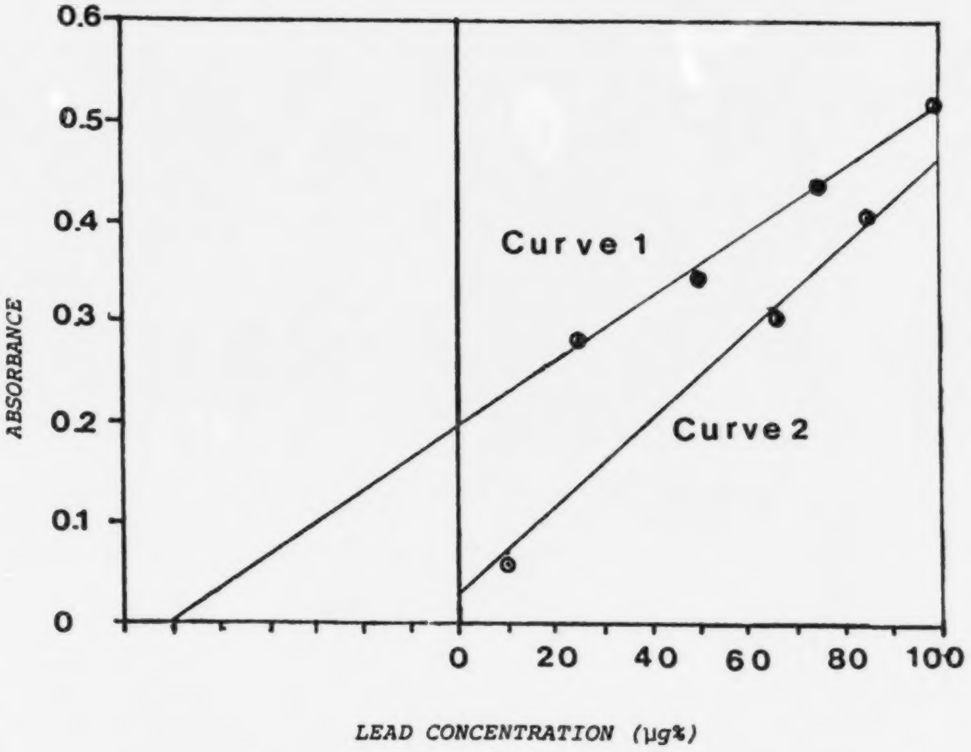
Original graphite furnace temperature programme.

Step No.	Temperature (°C)	Time (s)	Gas Flow (L/min)	Gas Type	Comments
1	75	2	3	Argon	Dry stage
2	95	15	3	Argon	Dry stage
3	140	10	3	Argon	Dry stage
4	300	8	3	Argon	Ashing
5	450	7	0.5	Air	Ashing
6	480	10	0.5	Air	Ashing
7	480	5	3	Argon	Ashing
8	480	1	0		Gas stop
9	2600	1.1	0	Argon	Atomization
10	2600	1	0	Argon	Atomization
11	2600	2	3	Argon	Tube clean

Table 7.

Modified graphite furnace temperature programme.

Step No.	Temperature (°C)	Time (s)	Gas Flow (L/min)	Gas Type	Comments
1	75	2	3	Argon	Dry stage
2	95	20	3	Argon	Dry stage
3	140	15	3	Argon	Dry stage
4	300	10	3	Argon	Ashing
5	450	7	0.5	Argon	Ashing
6	480	10	0.5	Argon	Ashing
7	480	5	3	Argon	Ashing
8	480	2	0		Gas stop
9	2000	1.1	0	Argon	Atomization
10	2000	1	0	Argon	Atomization
11	2000	2	3	Argon	Tube clean



CURVE 1: Standard Addition (Representative Sample)
CURVE 2: Interlaboratory Standard Calibration

FIGURE 2. Standard Addition and Interlaboratory Standard Calibration Curves.

Table 8.

Blood lead values: Original and modified versus interlaboratory results.

Sample No.	Original Methodology		Modified Methodology		Interlaboratory Program	
	Value (µg%)	RSD (%)	Value (µg%)	RSD (%)	Value (µg%)	RSD (%)
1	15.1	27.8	12.5	37.6	12.7	31.5
2	34.0	14.4	32.5	77.3	32.6	15.6
3	12.6	25.4	4.4	77.3	10.5	59.1
4	60.4	11.8	42.5	16.3	41.4	7.7
5	74.4	10.1	56.3	10.3	57.0	8.4
6	10.6	35.8	18.1	7.7	19.9	14.1
7	50.3	10.5	44.4	10.8	38.0	8.4
8	44.4	9.5	28.1	13.2	32.8	10.1
9	8.4	34.5	3.1	54.8	8.9	31.5
10	11.7	32.5	15.0	16.7	12.6	31.8
11	25.9	12.0	6.8	57.4	12.0	24.2
12	32.7	9.1	61.1	10.6	55.8	15.8
13	60.2	11.6	47.7	12.0	44.9	12.9
14	39.8	9.1	37.4	18.2	34.6	14.7
15	43.6	8.5	77.0	4.2	71.4	11.3
16	70.0	10.7	56.2	8.2	59.3	12.9
17	32.8	8.6	11.7	9.1	22.2	16.2
18	28.7	8.0	42.1	10.7	48.2	7.1
19	43.1	12.4	20.8	5.2	22.0	16.8
20	59.0	10.4	46.1	23.6	44.0	13.0
21	60.4	8.6	66.1	8.5	58.7	8.9
22	50.6	7.6	43.5	8.2	48.6	7.6
23	36.3	8.5	24.6	10.6	34.8	14.4
24	22.6	10.5	16.3	13.7	19.9	14.6
25	10.6	12.4	18.1	11.7	20.6	23.8
26	9.3	19.8	7.7	12.7	12.4	21.0
27	54.3	10.9	46.2	8.5	46.7	12.8
28	70.9	10.9	51.3	13.1	43.8	13.2
29	32.4	12.4	53.7	5.2	50.0	16.0
30	30.0	8.0	28.0	10.7	37.4	7.5

A Pearson correlation coefficient calculation was used to compare the values obtained with both the original and the modified programmes with the results of corresponding samples from the independent interlaboratory programmes. This calculation shows that there is poor analytical correlation between the original methodology values and the interlaboratory values. This result is summarized in Table 9 and Figures 3a-c.

Table 9.

Statistical summary.

Comparison Sets	Correlation Coefficient
Modified versus original	0.753
Original versus interlaboratory	0.752
Modified versus interlaboratory	0.975

Discussion

GFAAS is regarded by many as the method of choice for the routine laboratory analysis of lead in blood. However, unique and disparate methodological problems within this analysis must be resolved before it can be implemented with confidence for clinical use.

Although it has been shown that some GFAAS methods involving standard addition calibration are adequate for the detection of lead in blood (Brodie and Routh, 1984), all involve the time-consuming standard addition steps. The modified method, however, uses physiologically bound lead in blood samples as calibration standards. The only pre-treatment step in the modified programme is the simple addition of Triton X100. As a result, up to 30 samples per hour can be analysed.

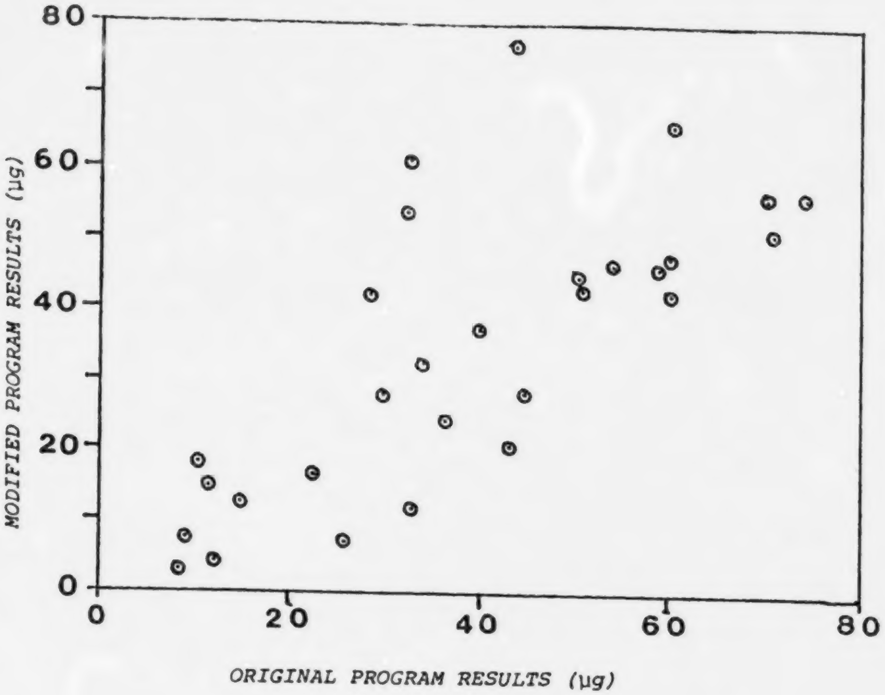


FIGURE 3A. Modified Versus Original Program Blood Lead Results

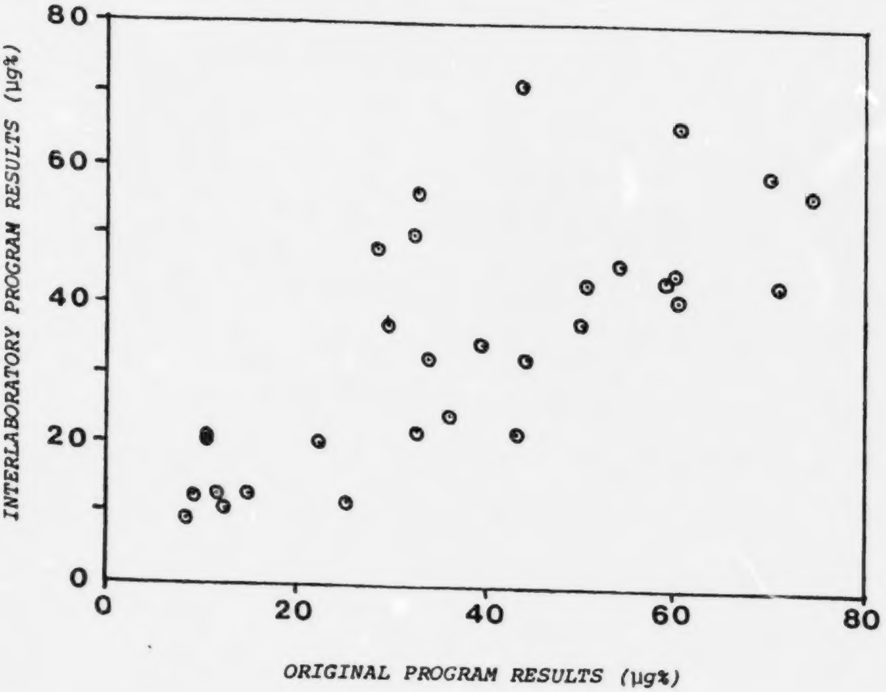


FIGURE 3B. Interlaboratory Versus Original Program Blood Lead Results.

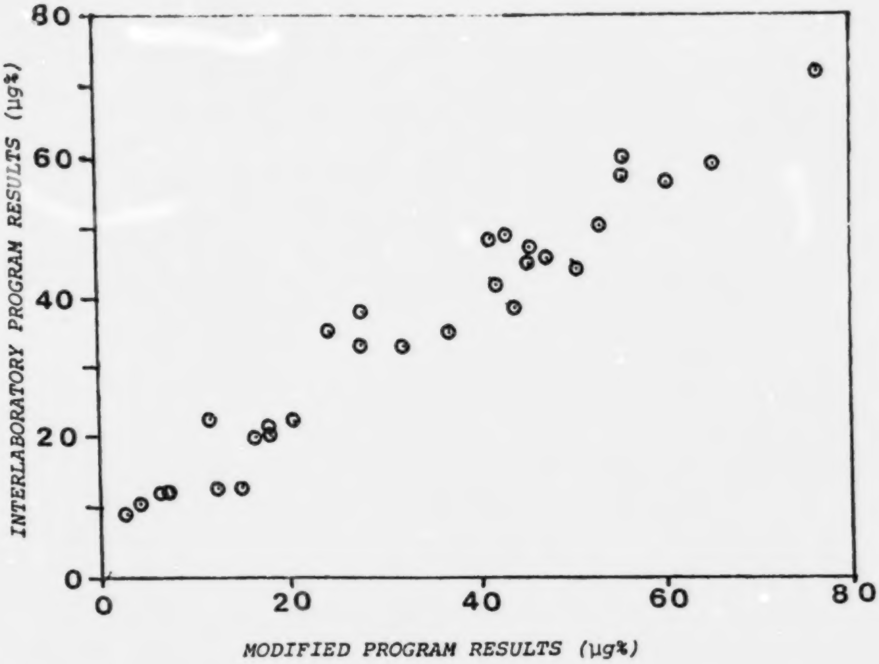


FIGURE 3C. Interlaboratory Versus Modified Program Blood Lead Results.

When the interlaboratory reproducibility of other GFAAS blood lead programmes and alternative blood lead analysis methods (Weber and Nantel, 1985) are compared with the reproducibility of the modified programme results, the modified GFAAS programme has equivalent or better reproducibility.

Interlaboratory programmes are invaluable for defining the precision of blood lead analysis methods. Table 10 shows recent results from an interlaboratory blood lead analysis program (41 laboratories) (Weber and Nantel, 1985). Of the methods used, over 50% was GFAAS, with the remainder being ASV, AAS with APDC-MIBK extraction and Delves Cup methods. Very wide ranges of the reported values per sample are evident, indicating that blood lead analysis remains relatively imprecise. It is not without significance to note that the laboratories involved in the programme are among the most reputable in North America.

Table 10.

Individual blood lead values (µg/L).

	Sample 1	Sample 2	Sample 3
	265	476	90
	240	410	90
	230	450	70
	205	391	67
	265	418	75
	253	417	151
	304	516	188
	224	377	80
	290	460	120
	228	414	85
	270	443	92
	205	368	79
	251	417	92
	190	350	100
	130	255	30
	264	401	85
	245	400	104
	200	390	60
	280	380	60
	194	400	62
	230	390	80
	183	346	86
	260	448	73
	242	420	84
	180	270	80
	246	429	84
	224	369	63
	175	283	87
	201	322	78
	190	320	70
	222	387	81
	227	418	82
	120	235	80
	186	394	0
	266	409	88
	180	395	80
	194	412	72
	203	349	65
	180	370	30
	250	450	75
	275	355	130
Target value (average)	225	395	80
Range (lowest to highest)	130-304	235-516	0-188

It is quite apparent that additional improvement is required with regard to the accuracy and precision of blood lead analysis. IDMS is a method which could possibly be used to determine the accuracy of routine blood lead analyses, including GFAAS.

This report is the result of experience with the Varian GFA 95 graphite furnace and the Varian AA 875 spectrometer, but the parameters discussed apply to blood lead analysis with any GFAAS instrument. The modified programme could easily be adapted to many other GFAAS instruments without resorting to special alterations. The results indicate that a balanced combination of (i) contamination control, (ii) moderate blood sample dilution and hemolysis, (iii) pyrolytically coated graphite furnaces with the insertion of L'vov platforms, (iv) flexible temperature and gas flow programming, (v) optical background correction facilities, (vi) high-speed spectrometer electronics, and (vii) calibration by a method other than standard additions is necessary to develop an efficient and effective GFAAS blood lead analysis programme.

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4. LEAD CONTAMINATION OF THE CANADIAN ENVIRONMENT

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Production and Consumption of Lead

Canada is one of the leading producers and a major exporter of lead in the western world. Lead production increased from about 200,000 t/a in 1960 to over 400,000 t/a in 1971, and has subsequently declined to about 300,000 t/a at the present time (Energy, Mines and Resources Canada, 1970-83). The lead export trend closely matches the production trend, as lead consumption in Canada has remained fairly steady at about 100,000 t/a since 1965 (Figure 1). The production of lead is a major industry in Canada, with an annual gross revenue of about $280 million in 1983. It provides employment to several thousand persons, most of whom are liable to become occupationally exposed to lead.

The manufacture of automobile batteries accounted for 50% of the 98,000 t of lead consumed in Canada in 1980. During this year, about 11,000 t of lead were used in the production of gasoline additives. It is estimated that about 30-35% of the lead consumed in a particular year is wasted in the environment.

Emissions of Lead

It is estimated that industrial activities released about 10,440 t of lead into the Canadian atmosphere in 1980 (Table 1). About 80% of the lead emissions came from automobile tail pipes, and about 17% was contributed by the mining and smelting of non-ferrous metals. The world-wide emission of

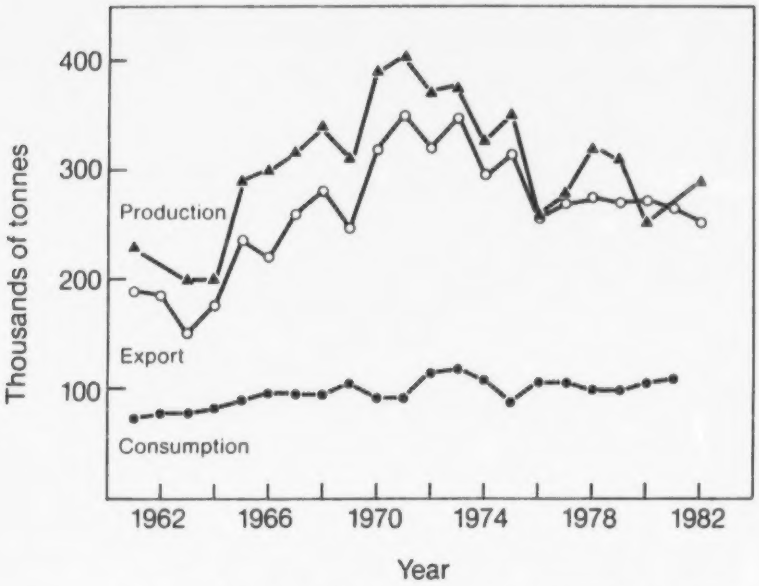

Figure 1. Production and Consumption of Lead in Canada

Table 1.

Atmospheric lead emissions for Canada during 1980.

Source Category	Consumption/ Production	Emission Factor	Lead Emitted (t)
Gasoline combustion	11x106 kg	75%	8270
Waste oil incineration	6x108 L	150 mg/L	90
Refuse and sewage incineration	2.5x106 t	25 g/t	62
Coal combustion	53x106 t	0.34 g/t	18
Heavy fuel oil use	24x109 L	0.5 mg/L	12
Wood burning	15x106 t	0.2 g/t	2.0
Lead mining and milling	296,410 t	750 g/t	222
Lead smelting and refining	296,641 t	1400 g/t	414
Secondary lead refining	162,463 t	550 g/t	89
Manufacture of lead goods	107,000 t	1200 g/t	128
Industrial applications of lead	107,000 t	300 g/t	32
Cu and Ni production	876,000 t	600 g/t	540
Zn production	1.1x106 t	450 g/t	477
Iron and steel production	16x106 t	1.5 g/t	23
Ferroalloys	2x106 t	3.5 g/t	7.0
Cement manufacture	9.8x106 t	0.1 g/t	1.0
Miscellaneous			50
Total			10,438

lead from anthropogenic sources during 1980 is estimated to be about 331,000 (Table 2), implying that Canada accounts for only about 3% of the lead released to the global atmosphere.

Direct industrial discharges of lead into Canadian waters are estimated to be only 610 t/a (Table 3). Except for local or restricted environments, direct industrial discharges are therefore unlikely to be a major source of lead in aquatic ecosystems. Indeed, numerous studies have shown that the lead in most natural water bodies is derived from the atmosphere (Edgington and Robbins, 1976; Nriagu et al., 1979; Evans and Rigler, 1985).

The release of lead to the soils of Canada is estimated to be about 71,000 t/a, most of which is derived from the mining sector (Table 3). In total, it is estimated that industrial activities currently release about 82,000 t of lead annually into Canadian air, water and soils (Tables 2 and 3).

Table 2.

Global versus Canadian emissions of lead to the atmosphere, 1980.

	Emission Rate (t)	
Source Category	Canada	World wide*
Gasoline and waste oil combustion	8,360	177,000
Waste incineration	62	8,900
Coal combustion	18	15,000
Lead production	725	34,000
Industrial applications of lead	160	7,400
Non-ferrous metal production	1,017	49,770
Iron and steel production	23	28,000
Wood combustion	3	4,500
Cement manufacture	1	50
Miscellaneous	69	5,900
Total	10,438	330,520

* Revised estimate from Nriagu (1979).

Table 3.

Anthropogenic release of lead to Canadian waters and soil in 1980.

Source Category	Emission Factor	Pb Released (t)
	Water:	
Lead mining and production	0.5 g/kg Pb	150
Industrial application of lead	1.25 g/kg Pb	125
Cu, Zn and Ni production	0.1 g/kg metal	200
Iron and steel production	0.5 mg/kg metal	8
Fossil fuel combustion	0.5 g/t fuel	26
Others	-	100
Total, water		609
	Soils:	
Lead mining and production	10% of lead ore mined	30,000
Industrial applications of lead	35% of lead used	35,000
Cu, Ni and Zn production	3 kg/t metal	6,000
Miscellaneous	-	500
Total, soils		71,500

Distribution of Lead in the Canadian Environment

Air

The geometric mean concentration of lead in urban areas of Canada has declined sharply in recent times, from about 0.79 μg/m^3 in 1970 to about 0.21 μg/m^3 in 1982 (Figure 2). The three-fold or so decline is also reflected at all the stations sampled, as evidenced by the comparable reductions in the 25th and 75th percentiles of the concentration distribution. The reduction in airborne lead levels has also been observed in the United States, where the average concentrations have also fallen from 1.2 μg/m^3 in 1970 to about 0.53 μg/m^3 in 1982 (Figure 3). It should, however, be noted that the most dramatic decline in Canada occurred between 1974 and 1978, and that the lead concentration is now falling only very gradually. By contrast, the average concentration in the USA was fairly steady between 1973 and 1977, and the sharp decline has occurred since 1978. The differences in the patterns of decline reflect the differing attitudes and regulatory controls in the two countries regarding the use of leaded gasoline.

The country-wide averages hide a number of important features about the distribution of lead in air. For example, the observed lead concentration is often strongly dependent on the sampling height. At one of the sampling stations in Montreal, the ambient lead level has fallen from 1.03 to 0.14 μg/m^3 between 1974 and 1982 at an elevation of 14 m, whereas the decline has been only from 3.78 to 0.78 μg/m^3 at height of 3 m (Table 4). In Toronto, one also finds a decline in airborne lead from 1.22 to 0.18 μg/m^3 at an elevation of 20 m compared with a drop from 1.72 to 0.66 μg/m^3 at a 1-m elevation (Table 4). Furthermore, the observation that the highest ambient concentrations are found at street level has to be a matter of some concern.

Table 4.

Effect of sampling elevation on ambient lead concentration.*

	Lead Concentration (μg/m^3)			
	Montreal		Toronto	
Sampling Date	14 m	3 m	20 m	1 m
1974	1.03	3.78	1.22	1.72
1975	0.86	2.62	0.91	1.34
1976	0.88	2.26	-	-
1977	0.69	1.61	-	1.22
1978	0.55	1.35	0.66	0.99
1979	0.46	1.36	0.44	0.75
1980	0.44	1.35	0.28	0.87
1981	0.38	0.63	0.45	1.10
1982	0.14	0.79	0.18	0.66

* Data presented pertain to Station Nos. 50108, 50109, 60401/2 and 60403 of NAPS (1974-83).

The ambient lead levels in the urban atmosphere show only a mild seasonal variation, with the concentrations during the months of August to December generally being higher than those during other months. The lowest concentrations are often found during the months of April to July (Figure 4). Likewise, in the United States maximum lead concentrations typically occur in winter, whereas minimum values are encountered in summer months (EPA, 1984). It should be noted that automotive emissions of lead should be higher in summer months because (i) gasoline consumption is usually higher in summer, and (ii) the lead content is often raised in summer gasoline to make up for the more volatile high-octane components that cannot be used in summer-time gasoline. The observed seasonal pattern thus suggests that there is less effective removal of the submicrometre plumbiferous particles in winter-time compared with the summer period.

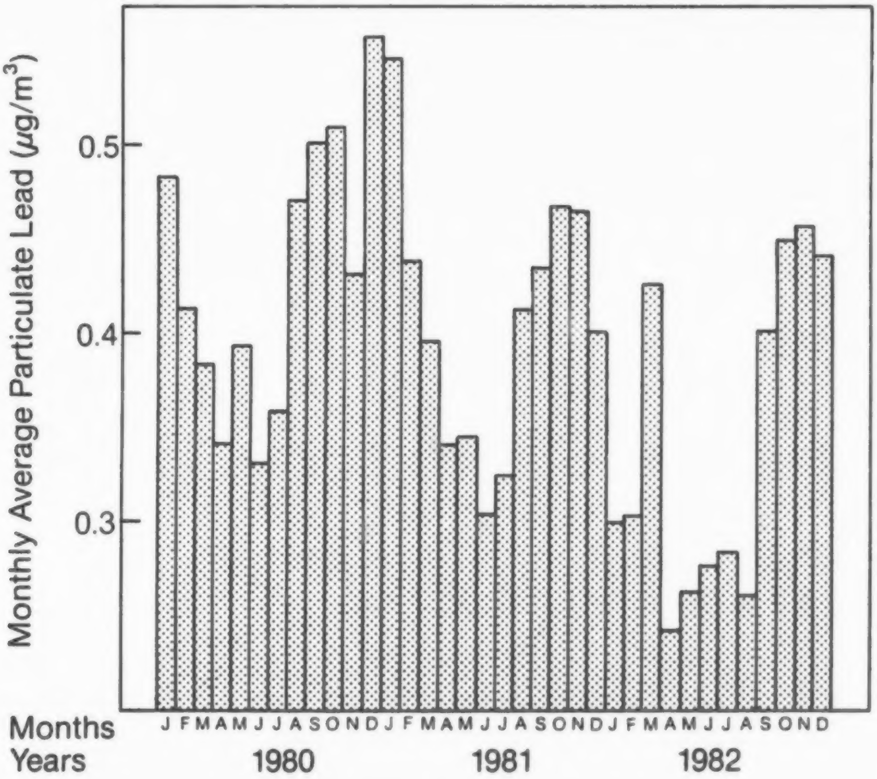

Figure 4. Urban Ambient Atmospheric Lead Levels

The lead concentration in Canadian Arctic air is about 1.0 $\mu g/m^3$, a value that is comparable with other data obtained at remote locations in the northern hemisphere (Table 5). It should not be surprising that the lead level in the Arctic is about 30-fold higher than the 0.027 $\mu g/m^3$ found in the less polluted Antarctica. In fact, the Antarctic concentration is comparable with the 0.05 $\mu g/m^3$ predicted for the pre-technological atmosphere (Nriagu, 1978; NAS, 1980; EPA, 1984). It follows that the present-day ambient lead concentrations in Canadian cities are about 4000- to 8000-fold higher than the expected level in the pre-technological atmosphere.

Table 5.

Atmospheric lead concentrations at representative remote locations (Wiersma and Davidson, 1985).

Location and Date	Pb Concentration ($\mu g/m^3$)
Montana, Glacier National Park; Aug. 1981	4.6
Washington, Olympic National Park; July/Aug. 1980	2.2
Canadian Arctic; late winter 1980	1.0
Greenland, Dye 3; Jun.-Aug. 1979	0.15
Greenland, Prins Christianssund; Jan./Feb. 1978	1.8
Greenland, Kap Harald Moltke; Jun.-Aug. 1974	0.2
Greenland, Thule; Feb.-Apr. 1978	8.0
Abastumani Mts., USSR; July 1979	1.0
Enewtak: Apr./May 1979	0.13
Jun.-Aug. 1979	0.096
Nepal, Himalayas; Dec. 1979	0.86
Chacaltaya Mts, Bolivia; Feb.-May 1976	3.7
Antarctica; Dec. 1974	0.027

Table 6.

Atmospheric lead fallout in Canadian cities (1982) compared with deposition rates in the polar regions.

Location	Fallout Rate (mg/m^2/a)
Sydney, N.S.	310
Glace Bay, N.S.	73
Montreal	203
Toronto	339
Hamilton	555
Sault Ste. Marie	86
Thunder Bay	146
London, Ont.	129
Winnipeg	593
Greenland	0.029
Antarctica	0.004

Atmospheric deposition of lead in the urban areas of Canada varies from under 80 mg/m^2/a recorded in Glace Bay, Nova Scotia, and Sault Ste. Marie to over 600 mg/m^2/a found at locations in Winnipeg (Table 6). At the present rate of deposition, the additional lead accumulated in urban soils during the next decade is expected to be 1-6 g/m^2/a. By comparison, the atmospheric flux of lead is 0.029 mg/m^2/a in Greenland and only 0.004 mg/m^2/a in the Antarctica. The spectacular deposition of lead in relation to the natural background rate justifies the reference to urban centres of Canada as 'hot spots' of lead.

Soils

Typical levels of lead in Canadian soils and dusts are summarized in Table 7. At present, anthropogenic sources account for about 60-90% of the lead in many urban soils in Canada. Notice that the lead content of many house dusts is so high that inadvertent ingestion of only a few milligrams of such material would be a health hazard to a youngster. In terms of its toxicity, it should further be observed that a large fraction of the lead in street dusts is preferentially concentrated in the very small particles (Sartor and Gaboury, 1984).

Table 7.

Typical levels of lead in Canadian soils and dusts.*

Sample	Lead Concentration (µg/g)	Anthropogenic Contribution (%)
Soils		
Remote	5-20	< 5
Rural	10-50	20-60
Suburban	50-300	60-90
Inner City	150-3000	60-95
Around smelters	Up to 3%	90-100
Street dusts		
Rural	30-500	< 60
Suburban	250-2000	< 80
Inner city	200-5000	< 80
House dusts		
Rural	20-80	
Suburban	50-400	
Inner city	150-3000	
Around smelters	Up to 5000	

* Compiled from the literature.

On the average, about 80% of the lead in street dusts of Halifax, Nova Scotia, is associated with carbonate phases and iron-manganese oxides (Table 8); the lead in such associations is potentially bioavailable. The accumulation of bioavailable lead in the fine particles supports the contention that house and street dusts represent an important pathway of lead exposure in urban children (Sayre et al., 1974; Schmitt et al., 1979; Duggan, 1983; Barltrop et al., 1975).

Table 8.

Speciation of lead in street dusts from Halifax, N.S.* (Fergusson and Ryan, 1984.)

Chemical Fraction	% Lead Extracted (Range)
Exchangeable	1.9 (0-6.4)
Carbonate	34 (20-53)
Fe-Mn oxides	44 (27-58)
Organic	7.1 (4.2-9.4)
Residual	11 (4.4-20)

* Total lead contents were 1920 µg/g in commercial areas and 674 µg/g in residential districts.

Water

The Great Lakes contain about 20% of the freshwater resources of the western world. Their basins are home to about 33 and 14%, respectively, of the Canadian and United States populations. These lakes thus provide an excellent illustration of the widespread contamination of Canadian freshwater resources with lead.

Atmospheric deposition of lead into all the Great Lakes is estimated to be about 4100 t/a, with fluxes into individual lakes being 650, 1730, 596, 754 and 379 t/a for Lakes Superior, Michigan, Huron, Erie and Ontario, respectively (IJC, 1980). These data correspond roughly to annual deposition rates of 8, 30, 10, 28 and 19 mg/m^2/a, respectively, in the basins of Lakes Superior, Michigan, Huron, Erie and Ontario. Atmospheric contributions account for 30-60% of total lead inputs into the Great Lakes, which exceed 7000 t/a (Table 9).

Table 9.

Mass balance for lead in the Great Lakes (all figures are in tonnes per year).

Input/Output	Superior	Huron	Erie	Ontario
Input				
Runoff and interconnecting channels	550	600	559	905
Shoreline erosion	?	?	437	50
Dredged spoils	?	?	99	65
Wastewater	4	8	?	?
Atmosphere	650	780	754	379
Total	1204	1468	1849	1399
Output				
Retained in sediments	1056	338	1131	471
Outflow, particulates	?	?	419	547
Outflow, dissolved	?	?	177	207
Total	1056	-	1727	1225

Because of the high pH values of the lake waters (typical range, 7.5-8.5), any soluble lead brought into the lake is quickly hydrolysed and removed as solid particulates. Nevertheless, the observed lead concentrations of 0.2-0.5 µg/L (Table 10) are quite typical of what one would expect in the less contaminated lakes and rivers in other parts of the country. The present concentrations of lead in waters of the Great Lakes are believed to be 10-90 times higher than estimated levels in pre-historic times.

Table 10.

Total lead concentrations in waters of the Great Lakes (Nriagu et al., 1981; Lum and Leslie, 1983; Rossmann, 1984).

Lake	Concentration (ng/L) A: Present-day	B: Pre-historic	A/B
Ontario			
Offshore	97	10	9.7
Nearshore	400	10	40
Toronto Harbour	930	10	93
Erie	240	10	24
Michigan	260	15	17
Huron	210	15	14

* The pre-historic data were estimated based on bedrock geology.

Table 11.

Lead content of plankton samples from Lake Ontario (Hodson et al., 1984).

Sample Location	Pb Concentration (μg/g) (range)
Net Plankton:	
Eastern Basin	4.7 (2.8-7.9)
Point Traverse	7.5 (3.5-12)
Cobourg	6.8 (6.0-8.7)
Port Credit	5.3 (4.8-6.0)
Niagara	29 (17-43)
Zooplankton (*Mysis relicta*):	
Eastern basin	2.0 (1.3-2.6)
Point Traverse	1.6 (1.2-2.4)
Cobourg	1.2 (0.9-1.6)
Port Credit	5.1 (4.4-5.8)
Niagara	4.5 (3.9-5.6)

The plankton communities in the Great Lakes show a propensity to bioaccumulate lead (Table 11). In general, the lead content of the net plankton is higher than that of the zooplankton. The lead concentrations in Great Lakes fish typically fall in the range of 0.2-0.6 µg/g (dry weight); the distribution of lead in Great Lakes biota has recently been reviewed by Hodson et al. (1984).

The sediments of the Great Lakes nicely document the recent sharp increases in the flux of lead into the lake basins. Recent studies show that present-day depositions of lead in sediments exceed the rate in pre-colonial times by about three-fold in Lake Erie, five-fold in Lake Superior, six-fold in Lake Huron and by nine-fold in Lake Ontario (Table 12). It is estimated that about 25% (Lake Huron) to 90% (Lake Superior) of the total lead input into the lakes is retained in the sediments (Table 9).

Table 12.

Enrichment of lead in the most recent sediments of the Great Lakes (IJC, 1977).

Lake	Average Pb Concentration (µg/g)	SEF*	Accumulation in Sediments (t/a)
Superior	44 ± 27	4.6	1056
Huron	49 ± 34	5.7	338
Erie	87 ± 50	3.4	1131
Ontario	107 ± 65	9.0	471
Georgian Bay	43 ± 34	5.8	-

* SEF = sediment enrichment factor.

Lake sediments have also been used to measure the regional differences in the rate of deposition of anthropogenic lead in various parts of Canada (Dillon and Evans, 1983; Evans and Rigler, 1985). The results (Table 13) show that the lead deposition is highest in south-central Ontario, where the time-integrated anthropogenic lead deposition ranges from 30 to 700 mg/m^2. The deposition rate decreases from this industrial zone, the lead flux rate at Schefferville, Quebec, being only 31-42 mg/m^2. The integrated deposition rate for lead pollution in Lake Huron is estimated to be 75 mg/m^2 (Table 13). These values document the large quantities of airborne lead that have been deposited even in rural and relatively remote parts of the country.

Table 13.

Sediment-derived all-time deposition of pollutant lead in different parts of Canada (Canadian data from Dillon and Evans, 1982; Evans and Rigler, 1985. Lake Huron data from Robbins, 1980).

Location (No. of Lakes)	Time-Integrated Lead Deposition (mg/m^2/a)
Muskoka-Haliburton (9)	677
Schefferville, Quebec-Labrador border (3)	44
Parc des Laurentides, Quebec (3)	333
Parry Sound, Ontario (6)	398
Barry's Bay, Ontario (6)	386
Southern Lake Huron	75

Undue Lead Insults from Different Environmental Sources

The preceding sections point to the widespread contamination of the Canadian environment with lead. The pervasive pollution has inevitably greatly increased the level of exposure of the Canadian population to lead. On the basis of the present-day environmental levels and the estimated pre-colonial concentrations, the exposures of contemporary Canadians can be compared with those of pre-colonial individuals (Table 14). It is suggested that the average Canadian daily absorbs about 30 times more lead than his or her pre-colonial counterpart. It is important to note that the data in Table 14 represent baseline exposures, and that large segments of the Canadian population supplement their daily lead intake by living in downtown areas or near smelters, from interior paints, from smoking and wine consumption, by eating produce from family gardens, as well as from occupational and secondary occupational sources. These undue lead insults, most of which come from automobile tail pipes, can add up to highly elevated lead burdens, with unknown health consequences for many Canadians.

Table 14.

Summary of baseline exposure of contemporary and pre-historic Canadians to lead (based on data from NAS, 1980; Squire, 1982; EPA, 1984).

Individual	Air	Water/ Beverages	Foods	Dust	Total Pb Intake (μg/day)
Child, 2 years old					
Contemporary, urban	0.5	6.9	33	14	54
Prehistoric	0.001	0.01	0.9	0.6	1.5
Adult female					
Contemporary, urban	1.0	5.5	45	3.5	55
Pre-historic	0.002	0.01	1.2	0.2	1.4
Adult male					
Contemporary	1.0	9.5	50	4.5	65
Pre-historic	0.002	0.1	2.0	0.3	2.4

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5. LEVELS OF LEAD EXPOSURE IN CANADIAN POPULATIONS

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Even though lead poisoning had been known for centuries, the interest accorded it was more or less cyclic over time. One such episode of increased attention to lead toxicity was the publication of Touguerel des Planches in 1839, reporting 1200 cases of lead poisoning. It was an era of rapid industrialization and the birth of new legislation aimed at the prevention of lead intoxication (e.g. the Factories Act in 1883) (Hunter, 1975).

After this phase of renewed interest, lead poisoning received very little attention until the late 1960's, when it reappeared as a real public health problem. Pediatricians became quite concerned about clinical cases of acute lead poisoning. Most of these were related to the high content of lead in paint used on indoor walls of houses, and even on children's beds and toys.

Mass screening programmes were set up in 1971 in the United States under the Lead-based Paint Prevention Act. These programmes multiplied across the United States during the last decade, as did epidemiological studies aimed at the study of other causes of lead overexposure. These studies were mostly concerned with the following aspects of the problem:

- point source emissions, especially in relation to primary or secondary smelters, battery recovery plants, mine tailings, etc.
- contamination of drinking water
- food as a source of lead body burden
- car emissions and their effects on air and soil contamination

- health effects of lead, especially the chronic low-level contamination of growing children.

The number of scientific papers on the subject increased considerably in both quantity and quality. As a result of this, both occupational and environmental standards were progressively tightened.

Unfortunately, this wave of public and scientific interest did not extend to Canadian communities, except in a few geographical locations, such as Toronto (MOE, 1975). Furthermore, most of the studies done in Canada were published in reports having only a limited diffusion, even in the scientific community, and almost none in the general public. This does not mean, however, that no research was done on lead in Canada. Many research teams, in fact, were very active in this field, but their research was oriented either toward the basic aspects of lead poisoning or to environmental contamination by lead, especially from industrial pollution.

This limited awareness of the lead problem in both the clinical and the epidemiological fields will be illustrated by the following four cases:

1) In 1975, the Science Council of Canada decided to set up a study on the decision-making processes in Canada that are designed to protect the public and the work-force from health hazards to which they might be exposed. The committee brought together to study the question decided to analyse six hazards in depth, one of them being lead (Science Council, 1977). Three background papers were prepared in order to help the work of the committee (Jervis, 1977; Stopps, 1977; Charlebois, 1977).

After reviewing the available literature, Charlebois summarized the situation very well: "No comprehensive survey of blood lead concentrations (PbB) in the Canadian population has yet been performed". He cited seven surveys of blood lead in Canadian children and adults, of which six were completed by Health and Welfare Canada and one by the Ontario Ministry of the Environment.

To explain this fact, Stopps concluded that:

> unlike most other industrialized countries, Canada has little history of health problems associated with lead. This is probably due, in part, to learning from other countries' mistakes, since industrialization generally occurred later in Canada than in Europe or the United States.

As we will see later, this may not be the only explanation, since one finds only what one looks for.

2) In the same year, 1975, an International Conference on Heavy Metals in the Environment was held in Toronto. Even though the issue of environmental and body burden of lead was addressed in length, the Canadian input was extremely scarce; one exception was the work of Roberts et al. (1974).

3) In 1978, the National Research Council of Canada published the report on lead of its Associate Committee on Scientific Criteria for Environmental Quality (Jaworski, 1978). Again, the literature was extensively reviewed, but still could not give a realistic picture of the Canadian situation as far as the level of lead exposure in the population was concerned. The discrepancy between the level of knowledge we have on the impact of lead on various species of plants and animals compared with man is well illustrated in that monograph.

4) In 1975, the Québec Department of Social Affairs gave a mandate to the Centre de Toxicologie du Québec to set up surveillance programmes for workers exposed to various toxic agents. The first programme to be set up was one on lead (Surveillances des Travailleurs exposes au Plomb).

Very soon after the implementation of this programme, hundreds of workers were found to be overexposed (blood lead levels in excess of 80 μg/dL) and even clinically intoxicated. Many of them had been sick for years, often having endured useless abdominal surgery. A significant number of non-occupational poisonings were also discovered, simply because blood lead level was then being offered to clinicians as a laboratory analysis option. Even now, we are still faced with industries paying compensation to large portions of their staff for having blood lead levels over 80 µg/dL. Most of these, however, are small- to moderate-size companies. The larger industries were able to reduce their average blood lead levels to values ranging from 40 to 70 µg/dL.

Our Centre has also completed a study on the contamination by heavy metals, including lead, of families living in the proximity of a smelter at Rouyn-Noranda, Québec (SPL, 1979). We also participated in a study in the vicinity of a similar primary smelter at Murdochville, Québec (Chenard, 1983).

In order to answer the question asked by the Commission on Lead in the Environment concerning "what reliable information have we about the level of lead exposure in the Canadian population", I will try to compare these fragmentary data with similar studies done in other countries. It is important, however, to keep in mind the serious limitations of the available Canadian data:

- these studies were not part of a systematic screening programme, so that some high-risk populations may have been missed
- except for the studies on point-source emissions, no efforts were made to identify the origins of the exposure (food, water, leaded paint, indoor dust, outdoor dust, traffic density, etc.)
- in many studies, the results were expressed as the arithmetic mean and the standard deviation of the mean, instead of geometric means,

percentiles or percentage of values that were found to exceed various guidelines

- the analytical methods differed from one study to another; we now know from proficiency programmes of interlaboratory controls that some analytical methods may give results that are consistently lower or higher than other methods.

Despite all these factors, we can still draw some preliminary conclusions:

1) The Toronto study (Roberts et al., 1974) on the impact of two secondary smelters on blood lead (PbB) levels in children living within 300 miles of two smelters (A and B) compared with controls showed the following facts:

- the arithmetic mean of the control group was 19 µg/dL and only 1% of the children in the group had PbB levels in excess of 40 µg/dL; this is quite comparable with levels in similar groups of children living in urban settings if they are not at high risk because of leaded paint
- the exposed groups had mean values of 27 and 28 µg/dL, respectively. In group A, sampled during the summer months, 20% had PbB levels in excess of 40 µg/dL. For group B, the sampling was done during winter months, and only 13% had levels above 40 µg/dL. These values are much lower than those found in the vicinity of a primary smelter in Idaho. The difference in climate may largely explain these differences, as well as the observations made in the Rouyn-Noranda and Murdochville studies.

2) The problem of young children living in old urban areas has been studied only in a very superficial way by Health and Welfare Canada. The results obtained, however, may be indicative of a situation quite similar to

the ones found in United States towns. For example, a survey done in Ottawa of 80 children with symptoms suggestive of lead exposure showed an average PbB level of 32 µg/dL. Of these children, 22% had levels between 30 and 39 µg/dL, and 30.7% had levels above 40µg/dL. A similar situation was found in Montreal (940 children randomly selected), but the levels were slightly lower. This clearly indicates the need for further investigation of the situation. We have no data on the evolution of these values over time.

3) In Rouyn-Noranda, the control population, which lived in a small town called Evain, showed an average PbB level of 12.2 µg/dL (min. 6.2, max. 21.2). Children living less than 1 km from the smelter showed an average PbB level of 15.2 µg/dL (min. 5.1, max. 37.1).

In Murdochville, the values were even lower. Children living in the town close to the smelter, with parents working at the smelter, had an average PbB level of 17.2 µg/dL, with a standard deviation of 4.4. The controls, who lived in Rimouski, a non-industrialized town, showed an average PbB level of 9.0 µg/dL, with a standard deviation of 2.7.

All these values are quite low compared with similar situations observed in United States studies. Both the control and exposed groups show PbB levels quite similar to those described in Denmark. We could speculate that climate plays an important role in reducing the level of exposure of young children to the lead in soil dusts.

One very significant source of exposure was found recently in Verdun, a suburban town of Montreal, when a lead-painted metallic bridge was being sandblasted. The lead content of the dust, measured in a densely populated neighbourhood below the bridge, averaged 3000 ppm. Many similar situations have occurred in different cities in the province of Quebec, but their impacts on health have not been studied.

Another question asked by the Commission was, "How accurate are lead determinations in blood and other tissues--air, soil, plants, etc.?". I will limit my comments to the measurements done in human biological samples, as Hamilton and Farant (p. 41) and Hammond (p. 27) are more familiar than I am with the other types of analysis.

Blood lead determinations can be very accurate if they are done by a specialized laboratory participating in good interlaboratory control programmes. Our Centre has been participating in such programmes for many years. We have also initiated such a programme on lead and other heavy metals, involving about 50 laboratories from different countries.

If we keep in mind the fact that PbB is a good indicator of the relatively recent level of exposure, it can be a good working tool. However, levels will vary significantly in the same individual from one season to another. This is why we must be careful when we compare the values found in different studies. As mentioned before, the technique used for the analysis is also important to consider.

Lead in urine is much more tricky to use unless we have a 24-h sample and the results are corrected for density or creatinine content. We ourselves use it not as an index of exposure but only to follow the effect of chelation.

Hair lead is theoretically an excellent way to measure the level of exposure over time, as we can cut it into small segments. We can then measure the variations from month to month. However, there are still serious limitations to this technique, because it is difficult to separate the external contamination from the internal intake of lead.

In recent years, two other tests have been developed to be used as indicators of the level of exposure to lead: (i) free erythrocyte protoporphyrin (FEP or ZPP), and (ii) aminolaevulinic and acid dehydratase (ALAD). These are treated in greater detail by Hammond (p. 27) and Hamilton and Farant (p. 41).

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6. BLOOD LEAD LEVELS IN CANADA: A COMPARISON WITH SOME OTHER COUNTRIES

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Body burden of lead in the human body has to be estimated by a proxy measure. Blood, hair, urine and tooth lead levels each have some value and some disadvantages. Other types of measurement which are more related to the effect of lead exposure than to body burden itself, such as free erythrocyte protoporphyrin, present additional difficulties. The response to a given lead dose may vary according to a variety of circumstances, including the competitive and/or additive effects of other chemicals such as calcium, magnesium, copper or cadmium.

The amount of lead excreted after chelation could theoretically provide one of the best estimates of lead deposited in the body tissues, in contrast to circulating lead. Unfortunately, very little is known regarding its applicability to population studies, and, more importantly, its use is not free of risk for the individuals tested. Lead levels in hair and in dentine have the advantage of reflecting a much longer period of exposure than blood lead, which reflects only recent (30-60 days) exposure. It is very difficult to get satisfactory results from hair measurements, however, because of the technical problems of external contamination. Lead levels in dentine are known to vary substantially depending on the selection of the tooth and of the site within the tooth; they can be used only within a limited age range in children, where tooth levels reflect lifetime exposure preceding the tooth fall.

Blood lead and free erythrocyte protoporphyrin levels are recognized as the most stable of the measurements discussed. They correlate quite well with one another, especially at levels of blood lead above 12 µg/dL. The accuracy of blood lead estimates at levels below 10 µg/dL is sometimes challenged, but blood lead is nevertheless the measurement of choice in epidemiological surveys.

The detailed reviews of analytical chemical methodology in blood lead determinations by Hammond (p. 27) and Hamilton and Farant (p. 41) allow us to reasonably assume that prior to the early 1970's the lower limits of detection (LLD) were around 10-12 µg/dL. This provides us with an aid in interpreting published survey findings of blood lead levels in different populations. The advent of the Delves Cups technology in atomic absorption spectrophotometry (AAS) and of anodic stripping voltammetry (ASV) in the mid-1970's had the effect of reducing the LLD to around 5 µg/dL, and it was only after the introduction of the AAS graphite furnace method that the validity of LLD's as low as 1 µg/dL could be accepted. Because of this problem, when comparing different surveys we have presented the data whenever possible as the proportion of children found to have levels above certain values. Such proportions remain stable even when the means may have been substantially shifted by the improved detection of lower values.

Only one survey has been conducted on a representative sample of the general population of this country: the Canada Health Survey (CHS, 1981), conducted during 1978-79. It reports on measurements of levels of blood lead, copper and zinc, as well as a number of health, socio-economic and life-style variables. The reliability of the lead measurements of the survey have, however, been criticized (Health and Welfare Canada, 1982). The most important criticisms cited include the relatively large number of zero values (which actually have to be interpreted as values below the lower limit of detection, rather than as zero), the suspected unreliability of the analytical method (ASV) at low lead values, the absence of a log normal distribution and a presumed loss of lead in the initial stage of collection (up to 24 h).

It is beyond the scope of this review to discuss such criticisms at length. We have analysed the relative performances of AAS (Delves Cups), AAS (graphite furnace) and ASV over the past 5 years, comparing all published results for which the target values were below 25 µg/dL, obtained from interlaboratory comparison, data published by the US Centers for Disease Control in Atlanta and data from other centres in Canada and the United States. These analyses indicate that, within the laboratory-to-laboratory variation, there is no reason to suspect a biased performance that would tend to give lower values in the majority of cases from the ASV compared with the other two methods (Table 1).

No *a priori* reason can logically be formulated as to why the distribution of blood lead levels in a general population should conform to a log normal form. In fact, it is unlikely that the distribution would conform exactly to any unitary form, as it is a mixture of diverse distributions in several sub-sets of the general population (age, sex, etc.). Additionally, it is mathematically certain that a data set containing zero values does not conform to a log normal distribution. We are not sure to what extent the degree of departure from a log normal distribution in similar data, such as the US National Health and Nutrition Examination Survey II (NHANES II), has been statistically analysed. In the CHS data, the addition of 5 before taking the log makes the distribution reasonably normal in the ranges above the median

Table 1.

Comparison of results of blood lead analyses from 1980 to 1984 from various interlaboratory comparison centres.*

Target Value	AAS--Graphite Furnace (Standard) $\bar{x}$	±s.d.	AAS--Delves Cups (NHANES II) $\bar{x}$	±s.d.	ASV (CHS) $\bar{x}$	±s.d.
3.0	5.7	3.8	6.8	2.7	4.1	2.9
4.0	4.2	2.2	4.7	1.5	4.2	3.0
4.0	4.0	1.9	4.3	1.8	4.9	2.6
4.0	4.0	2.5	4.3	2.3	4.8	2.5
4.0	3.5	1.7	4.7	2.3	4.3	2.5
4.0	4.3	2.9	5.4	2.3	3.1	1.9
4.0	4.4	2.4	5.9	3.1	4.5	2.9
5.0	4.4	2.6	5.8	2.0	3.8	2.7
6.0	4.8	2.5	5.6	1.7	4.1	2.9
6.0	6.6	2.3	8.5	3.2	6.0	2.5
7.0	7.2	1.2	8.6	1.9	5.8	3.8
8.0	7.7	1.2	10.7	3.5	5.8	3.8
10.3	10.2	na**	14.5	na	5.8	na
13.0	12.9	na	12.9	na	9.7	na
13.5	13.3	na	13.5	na	11.5	na
14.0	12.9	3.5	13.7	2.7	11.5	4.7
14.4	14.7	na	13.3	na	11.1	na
17.0	19.5	3.0	20.3	3.5	18.6	4.1
18.1	18.5	na	19.4	na	15.2	na
19.0	18.7	2.5	20.1	2.9	16.5	3.8
19.0	20.2	3.1	20.7	4.7	17.5	4.0
20.0	23.8	3.2	24.0	4.4	22.3	4.7
22.0	23.3	3.0	21.5	4.2	21.2	3.0
23.0	23.4	2.6	22.9	2.6	22.7	2.9
24.0	23.1	2.3	24.1	1.8	22.2	3.8
24.0	30.1	5.9	27.6	2.7	29.9	6.0

* Means and standard deviation of participant results compared to target values below 24 (μg/dL).

**na = not available.

Sources: Data abstracted from CDC Atlanta Blood Lead (Toxicology) Proficiency Testing Program, IDL (Wisconsin) and the Centre de Toxicologie du Québec (St. Foy). For this centre, the target value is represented by the mean of all values.

values and at zero. To obtain a good figure at lead levels of 5, 4, 3, 2 and 1, it would be necessary to add progressively larger amounts (up to 6.8) before taking the logarithms.

If the reason why this additional transformation improves the fit is that stated in the criticism (i.e. a loss of lead to the glass walls of the container in the first stage of storage), it would be necessary to postulate that the greater absolute loss of lead would occur with specimens which contain the least amount of lead (i.e. below 5 µg/dL). It should also be noted that the shape of the curve obtained by adding 1 or 5 to the lead values of the CHS (before taking the log) is remarkably similar to that obtained using log transformed data from the Kamloops survey (which the critics accepted as 'valid' data) (Figures 1, 2 and 3).

The scientist responsible for the chemical analysis could not accept the suggestion of a loss of lead during the first 24 h of refrigerated storage. The blood collection routine used in the CHS was the same as that used in NHANES II, where vacutainers (lavender cap, in this case) were also used. The laboratory scientists feel that values below 5 µg/dL obtained by their ASV procedure, which was primarily meant to screen for high values, cannot be considered too reliable. In the CHS sample, there were 927 adults (age 20+) with blood lead levels below 5 µg/dL. Uncertainty about the true lead levels of subjects with such values must have some effect on the precision of the estimated population mean; the additional error, however, cannot exceed ±0.85 µg/dL.

Another observation which encouraged us to accept the validity of the very low measurements was the very significant shift in the distribution of lead levels between males and females in the CHS sample. This shift of the

Figure 1

Standard deviates of the cumulative frequency distribution of log (n) values of Pb

Kamloops Male Children

(data from Subramanian and Meranger, 1983)

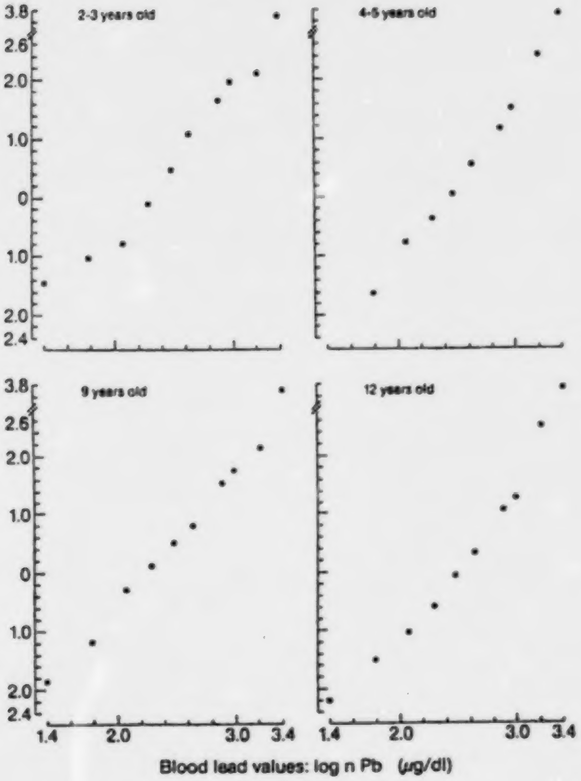


Figure 2

Standard deviates of the cumulative frequency distribution of log (n) values of Pb

Kamloops Female Children

(data from Subramanian and Meranger, 1983)

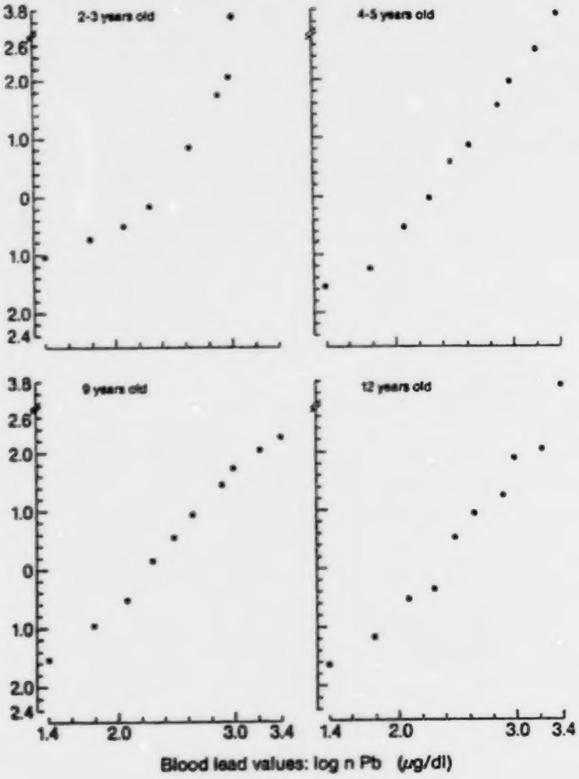
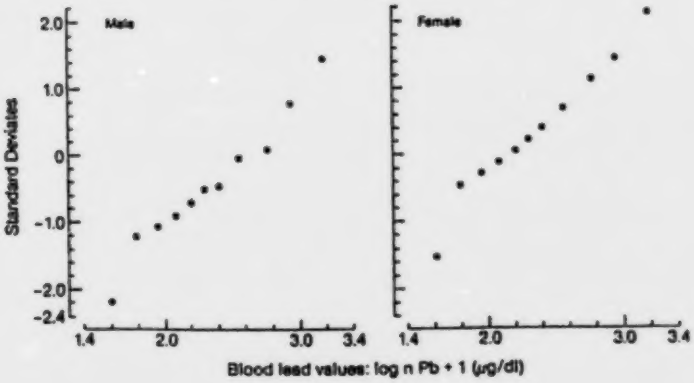


Figure 3

Standard deviates of the cumulative frequency distribution of log (n) values of Pb

Canada Health Survey 1978-1979

Male and Female aged 25-64 years old



ratios starts from the very lowest values and continues regularly up to the highest. This cannot be explained by random error from laboratory determinations, as it would apply equally to both sexes (Table 2).

Table 2.

Number of individuals by sex and sex ratios by levels of blood lead (μg/dL), Canada Health Survey 1978-79, all ages.

Pb Range	Male	Female	Male/Female Ratio
0	65	180	0.34
1	259	609	0.42
2	89	143	0.62
3	121	145	0.83
4	131	167	0.84
5	113	56	0.72
6	282	306	0.92
8-10	409	293	1.40
11-15	434	245	1.77
16-20	169	78	2.22
21-35	91	26	3.50
36-47	10	1	10.00

Whatever conclusions may be drawn from the above discussion, the fact remains that estimates for the Canadian population based on numbers (or proportions) of individuals with blood lead levels of 10 μg/dL and above remain valid, as only the values below 5 μg/dL might be in question.

Blood Lead Surveys in Canada

What follows is a review of the results from recent representative blood lead surveys conducted in Canada and elsewhere on non-occupationally exposed populations. These different surveys were conducted by various investigators who examined particular sections of the Canadian population; they contribute to a somewhat fragmented but accurate and methodologically sound portrayal of the extent of lead exposure in Canadians.

Wigle (1973) analysed the blood of 712 children up to and including 6 years of age (405 boys and 307 girls) who attended the Pediatric Out-patients' Department of the Montreal Children's Hospital. Blood was obtained by fingerprick, but a venipuncture was also done as a control if the result was high; of the 34 children whose initial concentration was above 40 µg/dL, only 7 concentrations were confirmed by venipuncture. The fact that the study sample comprised children attending hospital clinics makes the interpretation difficult, and may indeed bias the results; 8.7% of males between 2 and 4 years of age showed blood lead levels higher than 40 µg/dL (Table 3).

In a second study in Halifax (Wigle, 1973), capillary blood samples were obtained from 184 children in a similar manner to that carried out in Montreal. One hundred and twenty-nine children had blood lead levels between 0 and 29 µg/dL (95.7%), six between 30 and 39 µg/dL (3.2%) and two between 40 and 49 µg/dL (1.1%).

Another survey was done in Toronto (Roberts et al., 1974). Capillary blood was obtained from two groups of children less than 15 years old and living within 300 m of two secondary lead smelters (sample 1 in summer, 2 in winter). The results were compared with those from a group of children living in an urban area (sample 3). Some 20% of the children living close to the smelter were found to have blood lead levels greater than 40 µg/dL compared with only 0.5% of 1255 adult females living in the same area, and 1% of the children living in the non-industrial areas of the city. This study confirmed the importance of environmental dust as a lead source for children, especially in the summer months.

Neri et al. (1978, 1984a) undertook a survey in Trail and Nelson, British Columbia, in May 1975. Trail is a smelter city, and Nelson a compara-

Table 3.

Levels of blood lead (µg/dL) in surveys in Canada.*

Area	Year	Age Group	Males Mean	Males %>20	Males %>40	Females Mean	Females %>20	Females %>40	Both Sexes Mean	Both Sexes %>20	Both Sexes %>40
Montreal (P.Q.)	1973	0-2			8.1			7.8			8.0
		2-4			8.7			6.8			7.9
		4-6			3.4			0.0			2.1
Halifax (N.S.)	1973	Children									1.1
Toronto (Ont.)	1973	0-15 sample 1								27.0	20.1
		0-15 " 2								28.0	13.0
		0-15 " 3								19.0	1.0
Trail (B.C.)	1975	1-3							22.0	56.2	4.1
		Grade 1							22.0	58.4	0.9
		Grade 9							11.0	4.3	1.4
Nelson (B.C.)	1975	1-3							14.0	7.3	0.0
		Grade 1							11.0	10.4	0.0
		Grade 9							10.0	1.0	0.0
Ottawa (Ont.)	1975	0-6	21.1			18.7					
		7-14	15.6			15.0					
		15-34	14.3			11.9					
		35-64	16.5			13.1					
		65+	13.7			11.8					
Kamloops (B.C.)	1977	2-3							10.8	5.5	
		4-6							11.6	6.5	
		7-9							11.0	5.6	
		10-12							12.4	9.7	
	1977	Cord blood							5.0		
	1978	"							5.0		
	1979	"							6.0		
	1980	"							4.0		
	1981	"							5.0		
	1982	"							4.0		
	1983	"							10.0		
Toronto: South Riverdale (around smelter area)	1982	0.5	14.3			13.6			14.0	13.3	3.0**
	1983	0.5	15.4			16.2			15.8	18.6	4.3**
	1984	0.5	15.0	14.8	5.3	15.8	21.5	6.6	15.5	18.5	6.0**

* See text for references.

** >25 µg/dL.

ble city 45 km away that has no lead-handling industry. Duplicate samples of capillary blood were obtained from younger children and venous blood from older children and adults; lead levels were measured by anodic stripping voltammetry. Three age groups of children were studied: 1-3 years old, 6 years old and 14 years old. In Nelson, the numbers in each group were, respectively, 55, 92 and 101, whereas in Trail they were 95, 106 and 138. The two younger age groups in Trail averaged 22 µg/dL, well above their age peers in Nelson (14 µg/dL). Trail Grade 9 children, however, who were less exposed to dust, averaged 11 µg/dL, only marginally higher than their peers in Nelson (LLD in this survey was 5 µg/dL). Results for occupationally exposed groups in Trail are omitted in this review, but the mean levels for adults without occupational exposure were found to be 12 µg/dL in both Trail and Nelson.

Another study was conducted in Ottawa in 1975 on a sample of 652 individuals (Wigle and Charlebois, 1978), 213 of these being under 16 years of age. The results showed that blood lead levels increased with age from age 7 up to age 64 for both sexes, dropping considerably for the over-65 age group. Levels above 30 µg/dL were found in 6 children up to six years of age (8%) and in four of the seven children up to 14 years of age (3%); all were found to have lower values on follow-up with venipuncture. These levels are generally lower than those found in Montreal. Differences in sampling and possibly improved analytical techniques may be responsible for the differences.

In Kamloops, British Columbia, Neri et al. (1984b) examined the blood lead levels of 1048 children aged 2-12 years. The mean lead levels ranged from 10.8 to 12.4 µg/dL, and the proportion of children with levels above 20 µg/dL was 7%. In addition, lead in the umbilical cord blood of deliveries at the local hospital was measured during the 7-year span from 1977 to 1983.

Table 4 shows the results for what is, in fact, the only Canadian study to date designed to examine temporal trends. Consumption of gasoline containing lead for the same years was obtained from the Petroleum Association for the Conservation of the Environment for comparison (see Table 4).

Table 4.

Mean lead levels of cord blood (μg/dL) and leaded gasoline consumption (million litres) by year, Kamloops, B.C.

Year	N	mean	Gas Consumption
1977	19	5	12.98
1978	486	5	14.75
1979	90	6	148.86
1980	105	4	81.12
1981	101	5	80.81
1982	60	4	65.52

The increase in consumption of lead gasoline during the period of activity of the mining-smelting complex did not seem to have an effect on the levels of lead in the cord blood of local residents.

Ellis et al. (1985) examined blood lead levels in children in 1982-83 and again in 1984 in South Riverdale, a Toronto community situated next to a secondary lead smelter. The survey was conducted by the University of Toronto in co-operation with the City of Toronto Department of Public Health. One hundred and thirty-five children of less than 6 years of age were tested in 1982, 70 in 1983 and 216 in 1984. The results indicated that in 1982 13.5% of children in South Riverdale had blood lead levels higher than 20 μg/dL, a higher proportion than that in a sample representative of the general population of Ontario, although not as high as that found in Trail in 1975. The results for South Riverdale were 13.6% in 1982, 18.6% in 1983 and 18.5% in

1984, compared with 56.5% for Trail children.

Savoie and Weber (1979) made an interesting and comprehensive study in the north-eastern region of Quebec in the vicinity of Rouyn-Noranda, where there is a lead mining and smelting complex. A sample of 512 children and adults was tested for blood lead, erythrocyte protoporphyrin and ALAD activity. Rouyn was divided into three areas according to proximity to the smelter. Two nearby rural localities (McWatter and Evain) and two control towns (Val d'Or and Ville Marie) were included in the study. Table 5 shows the results of blood lead measurements; only the results for non-occupationally exposed individuals are presented. Zones 1 and 2 were found to have higher blood lead values than Zone 3 for all age groups. Children aged 0-12 years had higher lead levels than adults in all but Zone 3. The importance of lead in dust is clearly shown by the much higher levels of those children living in Zones 1 and 2. These results emphasize the importance in Canada of the so-called 'hot spots'--relatively limited areas around industrial complexes where high levels of lead are found.

Table 5.

Blood lead levels (μg/dL) by age and exposure zone: Rouyn, 1979.

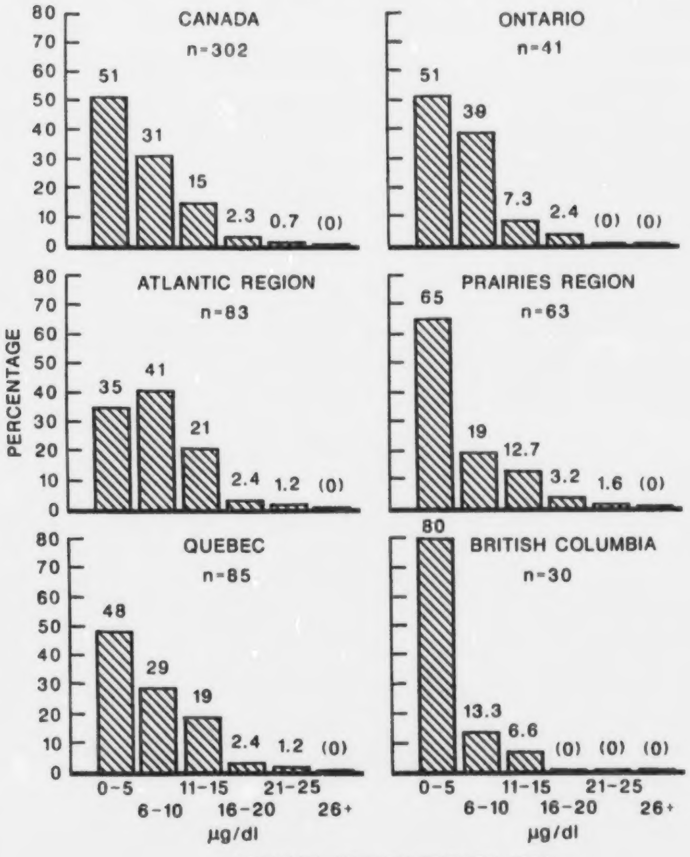
	Rouyn-Noranda												Ville	
Age	Zone 1		Zone 2		Zone 3		McWatter		Evain		Val d'Or		Marie	
Group	N	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$
0-12	7	25.3	5	25.0	12	16.3	4	17.3	5	17.0	11	15.4	9	14.2
13-20	18	20.6	15	19.8	14	17.2	5	15.5	-		22	12.7	16	11.9
21-60	38	22.6	53	21.9	62	19.5	17	16.2	15	16.8	71	16.0	48	16.3
>60	8	21.8	18	18.3	10	15.4	1	18.7	1	18.1	12	14.1	9	14.6

Chenard (1983) examined 327 children of 6-12 years of age in Murdochville, Quebec, where there is a copper smelter, and in a comparison town. The child population was divided into four exposure groups. Group I consisted of children residing in Murdochville having one parent employed at the smelter, children in Group II resided in the town but neither parent worked at the smelter, Group III children had one parent working at the smelter but lived outside the town and Group IV was a control, with children living more than 200 km away (St. Robert de Rimouski, Quebec). Higher levels were found in the first two groups, with a mean of 16.6 and 16.3 µg/dL for Groups I and II, respectively. Only in these two groups were levels above 25 µg/dL found (3% and 4%, respectively, for Groups I and II). The mean blood lead levels for Group III was 11.2 µg/dL, and for the control group 9.1 µg/dL. It appears again that the greatest influence on blood lead levels in children comes from dust.

The Canada Health Survey was undertaken in 1978-79 (CHS, 1981). In this survey, blood lead measurements were made on individuals 3 years of age and older. For comparison purposes Neri and Hewitt (1986) have used the actual values of the sample and not their weighted contribution to the total Canadian population. As discussed before, the least debatable estimates are represented by the proportions of individuals having blood lead levels above 10 µg/dL. Table 6 and Figure 4 show the results for children 3-9 years of age for Canada as a whole and for the five regions established for the CHS: Maritimes, Quebec, Ontario, Prairies and British Columbia. The proportion of children with blood lead levels above 20 µg/dL was 0.7% for all Canada (4.4% for males aged less than 4). No children in Ontario and British Columbia were found to have blood lead levels above 20 µg/dL, whereas in Quebec, the Atlantic and Prairie regions 1.2, 1.2 and 1.6%, respectively, exceeded this value. No children at all were found to have blood lead levels above 25 µg/dL. All blood lead levels measured were venous and not capillary; the latter are more subject to contamination. By way of comparison, in the 1984 Niagara Street (Toronto) survey, three subjects (two children, one pregnant female) were found to have blood lead levels above 20 (one above 30) µg/dL by the finger-prick method. The levels obtained after retesting with venous blood were 11.1, 10.4 and 5.6 µg/dL (Ellis et al., 1985). In the 1985 survey in this area, 13 individuals were found to have blood lead levels 20 µg/dL or greater;

Figure 4

PERCENTAGE DISTRIBUTION OF BLOOD LEAD CONCENTRATION FOR CANADA* AND 5 REGIONS. CHILDREN AGE 3-10



*CANADA HEALTH SURVEY 1978

upon retesting of their venous blood, it was found that only one adult (a worker in the nearby lead industry) had a level of 41 µg/dL, and one child had a level of 20 µg/dL.

Blood lead levels for men were found to be higher than for women in all age groups. As well, men have a greater shift than women toward higher blood lead with increasing age. The largest levels are shown by men aged 35-54 years. Of interest is the shift in the frequency distribution of lead values between male and female subjects (Table 6), which shows an almost continuous change from the very lowest to the highest levels (see also Table 2).

Table 6.

Canada Health Survey - 1978: Percentages of males and females by age groups and by range of blood lead levels (µg/dL)

Age Groups	Males					Females				
	0-10	11-15	16-20	21-35	36-47	0-10	10-15	16-20	21-35	36-47
0-4	90.3	4.4	0.0	4.4	0.0	100.0	0.0	0.0	0.0	0.0
5-9	80.1	16.3	2.1	1.4	0.0	79.5	17.3	3.2	0.0	0.0
10-14	75.1	19.4	3.7	1.8	0.0	84.2	12.6	2.2	1.1	0.0
15-24	72.7	17.2	6.5	3.1	0.7	88.7	9.2	1.1	1.1	0.0
25-34	63.0	24.4	5.6	6.7	0.0	89.9	6.6	3.3	0.2	0.0
35-44	59.6	19.2	12.9	7.5	0.8	87.2	8.0	3.5	1.0	0.3
45-54	66.0	20.7	10.3	3.5	0.9	75.9	14.4	7.7	2.0	0.0
55-69	60.5	22.8	12.9	3.8	0.3	82.8	11.4	3.9	1.9	0.0
68+	72.3	18.1	5.2	3.9	0.7	84.6	12.4	1.9	1.2	0.0

The Ontario Survey (Ontario Ministry of Health, 1985) was done in 1984. It sampled urban, suburban and rural Ontario children from schools in selected cities. Kindergarten and Grade 1 children from four to six schools from each centre were invited to participate. The schools chosen were all close to air quality monitoring stations. A total of 1315 children aged 6 and younger was sampled. Siblings of the schoolchildren were tested in order to obtain representation of the younger children (<3 years), although this meant sacrificing some of the independence of the observations. The distribution by age is shown in Table 7, which indicates that the youngest age group had a slightly higher mean blood lead level. On the whole, the results from Table 8 show that the levels from the urban areas were higher than for the suburban and rural areas, a pattern observed in other studies. The CHS population sample is to some extent an overrepresentation of rural and remote areas. Because no adjustment has been made for this in the tables, the summary figures shown for the regions and for Canada as a whole would verge on the low side.

An unforeseen problem in interpreting the results from the rural areas in Ontario has been the finding that lead in the soil of three of the schools in one of the two rural areas (Dunnville) had lead levels higher than those found even in the suburban areas.

Table 7.

Distribution of blood lead concentration (µg/dL) by age among sampled Ontario children.

Age (Year)		Number	Median	Geometric Mean	± s.d.
3		166	11.04	10.99	3.9
4		257	10.29	10.15	4.4
5		471	10.39	10.36	4.5
6		427	9.69	9.74	3.5
All Ages	M	650	10.50	10.57	4.2
	F	619	9.89	9.74	3.9

Table 8.

Geometric means of blood lead levels (μg/dL) in the Ontario Survey, 1985.

Area	Age Group	Males Mean	Females Mean	Both Sexes Mean	Both Sexes %>20	Both Sexes %>25
Ontario	<6	10.5	9.7	10.4	4.2*	1.3
Urban						
Windsor		12.2	11.6	12.0	6.7	1.8
Toronto		12.4	11.6	12.0	7.7	1.8
Suburban						
Scarborough		10.8	10.0	10.4	4.2	1.6
Etobicoke		10.1	9.1	9.7	1.2	1.6
Rural						
Nanticoke-Walpole		10.1	9.5	9.95	5.2	0.8
Longwoods		7.9	7.5	7.7	1.2	0.8

* In all cases where children with blood lead > 20 μg/dL were retested by venous sampling, the levels were found to be lower. Of the few whose subsequent test remained above 20 μg/dL, most were subject to specific exposures in the home.

On the whole, the blood lead levels found in the Ontario Survey are fairly comparable with those reported for other places with no known nearby industrial sources of lead, such as Nelson and Kamloops in British Columbia.

Blood Lead Surveys in Other Countries

United States

Two surveys were conducted in the Silver Valley in 1974 and 1975 (Yankel et al., 1977). Children and adults were sampled at various distances from the smelter in Kellogg, ID. Table 9 indicates the importance of the distance from the source for the 1974 blood lead data. This is considered a 'hotspot', but the average levels for both children and adults are substantially higher than in similar areas in Canada (Neri et al., 1978).

The National Health and Nutritional Examination Survey was conducted in the United States between 1976 and 1980 (US Department of Health and Human Services, 1984). Blood lead levels were measured in subjects from 6 months through 74 years of age. Blood samples were analysed by the Delves Cups atomic absorption method. A sample of 16,563 people participated in the probability samples survey. Three groups of interest were oversampled: children aged 6 months to 5 years, persons 60-74 years and certain subgroups of special interest for a nutritional assessment.

Table 9.

Blood lead levels in the Silver Valley study (Yankel, 1977).

Area	Distance Km	Blood Lead Levels (geometic means) µg/dL					
		Children (1-9)		Teenagers		Adults	
		N	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$
I	< 1.6	174	65.6	20	39.3	83	37.7
II	1.6 - 4.0	204	47.4	38	33.3	192	32.6
III	4.0 - 10.0	193	33.8	24	27.9	49	29.7
IV	10.0 - 24.0	168	32.3	1	-	5	-
V	24.0 - 32.0	198	27.6	0	-	3	-
VI	72 logging	92	21.0	0	-	0	-
VII	72 previous mining	40	30.3	14	34.6	42	32.3

The means of blood lead levels are shown in Table 10. Men have higher levels than women; as well, black men and women have higher blood lead levels than whites in all age groups. White children from higher-income families and those residing in smaller urban areas were reported to have lower blood lead levels; this was confirmed by the proportion of children with blood lead levels above 30 µg/dL. Four per cent of all children were found to be in that category, 12% of blacks compared with 2% of whites. The highest proportion of children with such elevated blood lead levels was found among black children of low-income families (18.5%). Even in smaller urban and rural areas, more than 10% of black children had elevated blood lead levels, compared with less than 2% of white children. At a blood lead level of 20 µg/dL, one of two black children and one of five white children would have elevated blood lead levels. The results from the NHANES II (1976-80) are compared with those obtained in the CHS (1978) and the Ontario study (1984) in Figure 5. The proportion of children having blood lead levels near or at the intervention level (20 and 25 µg/dL, respectively) appears to be much lower in the Canadian children.

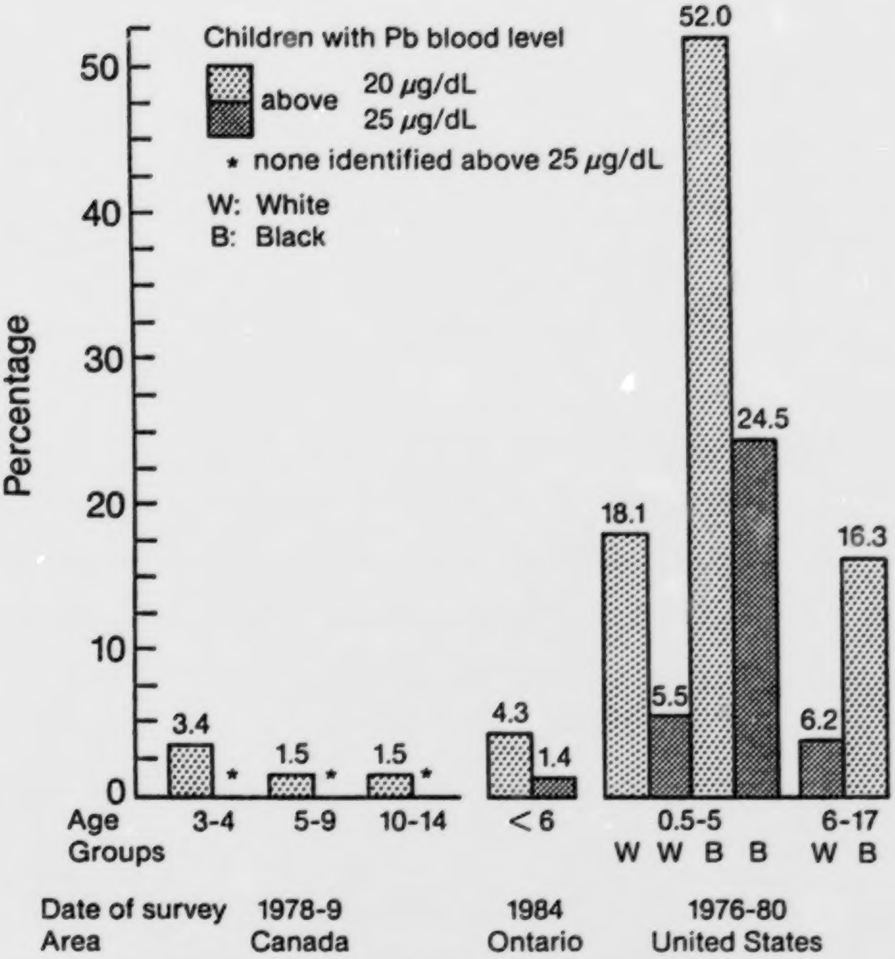
Angle and McIntire (1979) conducted a study on 831 children in Omaha, Nebraska. Their main objective was to relate blood lead levels to air lead concentrations. They chose three areas, an urban commercial area in the vicinity of a small battery plant (n = 132), an urban mixed-residential area

Table 10.

Geometric mean blood lead levels (µg/dL) and percentage above certain limits in the US NHANES*, 1976-80, by case and sex.

		Geometric Mean			%>20			%>30	
Age Groups	White	Black	All	White	Black	All	White	Black	All
6 mon - 5 yrs both sexes	14.0	20.9	14.9	18.1	52.2	24.5	2.0	12.2	4.0
6 - 17 yrs both sexes	12.1	14.8	11.7	6.2	16.3	7.6	0.4	0.7	0.5
18 - 74 yrs M	16.6	19.1	15.8	27.1	41.3	28.3	3.8	6.4	4.1
F	11.7	12.7	11.0	5.4	7.2	5.7	0.4	-	0.5

* Data projected to the US population.



N.B. Blood leads have been falling in many, if not all the countries shown.
Data from different time periods should only be compared with caution.
Figures above columns are actual percentages.

Figure 5 Comparison of children with blood lead levels above 20 and 25 µg/dL for Canada, Ontario and United States.

Source: Canada Health Survey (1981), Ontario Ministry of Health (1985), Annest (1983).

adjoining downtown Omaha (n = 589) and a suburban area (n = 110). A statistically significant difference was found in blood lead levels, with geometric means of 24.8, 22.0 and 18 µg/dL, respectively, for the three exposure areas. They also noted a decrease in all areas during the period 1971-75, but no changes between 1975 and 1977. The younger children had only marginally higher blood lead levels, the mean being 23.9 µg/dL for the age group 1-5 and 22.3 µg/dL for those aged 6-18 years.

The Detroit survey (Talbott et al., 1982) was conducted between January 1972 and December 1978. Blood samples from January 1972 through December 1973 were analysed by the dithiozone extraction-calorimetric method, and from August 1973 through December 1978 by atomic absorption spectrophotometry. A group of 27,430 black children from 15 socio-economically similar areas in central Detroit was tested (Table 11). Careful examination of the data reported shows that lower income, lower parental education and living in pre-1950 housing are factors linked to a higher blood lead level in children.

Table 11.

Mean levels of blood lead (µg/dL) in surveys in the United States.

Area	Year	Age Group*	Geometric Mean
Detroit	1973-1980	0-6	
		SE1	20.9*
		SE2	29.1*
Boston**	1979-1981	All	6.6*
		Summer	7.8*
		Winter	5.2*

* All = all races; SE1 = high socio-economic group; SE2 = low socio-economic group.
**Geometric means

Rabinowitz and Needleman (1982) reported on the umbilical cord blood lead of 97% of all live births occurring at the Boston Lying-In Hospital from April 1979 to April 1981 (Table II). Chemical analyses were done by anodic stripping voltammetry. The sample consisted of 11,837 consecutive births representing an ethnically and economically diverse population living in urban and suburban Boston. The mean for the entire sample was 6.6 µg/dL, with a range from 0.0 to 37 µg/dL. It is of interest to note that there was a decline of 11% per calendar year during the span of the survey. Also of interest is the difference between the cord blood lead levels in summer and in winter (7.8 and 5.2 µg/dL, respectively).

Australia

A study was conducted in November 1980 (Nolan, 1982); it included 324 students from Grades 2 to 6 of four primary schools within the boundaries of the Sydney City Council. The sample had been designed to test for poliomyelitis antibody status. The numbers of students from each school were 72, 121, 73 and 58. Blood samples were obtained by venipuncture. The results (Table 12) indicate that 2.1% of all children had levels above 30 µg/dL.

A survey in Queensland between May and November 1981 measured the blood lead levels of 514 children from 1 to 16 years of age (Rathus et al., 1982). The sample was selected from out-patient clinics of the Royal Children's Hospital for whom a venipuncture had already been ordered. Those children from whom a large sample of blood was to be taken or those who seemed unwell were excluded from the sample. The analyses were done by atomic absorption spectrophotometry. The highest blood lead levels were found in subjects aged 16, and the lowest were for children between 5 and 9 years of age; however, there

Table 12.

Levels of blood lead (μg/dL) in surveys in Australia (Bell, 1981; Nolan, 1982).

Area	Year	Age Group (yrs)	Number	$\bar{x}$	>20	>30
Sydney	1980	7-12				2.1
		School#1	72	17.8		
		#2	121	16.5		
		#3	73	13.4		
		#4	58	13.3		
Queensland	1981	1-4	42	11.0		
		5-9	210	8.7		
		10-15	229	10.1		
		16	3	16.7		
		All age groups	514	9.5	1.9	
Victoria	1980	Pre-school and school age	284	10.5	-	0.0
New South Wales						
Mosman Spring	1979	8	381	21.4	49.0	14.0
Autumn		8	242	18.8	37.0	5.0
Gardeners Road Spring	1979	8	400	24.8	68.0	25.0
Autumn		9	233	19.5	39.0	6.0
Port Kembla	1973-1979	<15	196	12.2	7.1	1.0
Cocklecreek	1973	<16	182	14.9	16.2	2.9

were only three 16-year-olds in the sample. Compared with the Sydney study, blood lead levels obtained in Queensland are much lower.

Another survey was done between 1973 and 1979 in New South Wales (Bell, 1981). The author reported on his own study and compared it with other studies on pre-school children and schoolchildren in Australia--the aim was to assess whether blood lead levels in Australian children met the 'acceptability' criteria of the European Communities directive and US Centers for Disease Control. Table 12 provides details of the results. Mosman is a surburban area and Gardeners Road an industrial one. Both are high-traffic and high-population-density areas. The spring-autumn difference shows the importance of taking into account the season in which blood is collected when making comparisons. Compared with Victoria, the more industrialized areas show higher blood lead levels. A small substudy done in Victoria is also of interest. Twenty children living close to major freeways were compared with matched controls: blood lead levels were 12.1 (±3.0) and 11.4 (±3.5) µg/dL, respectively, indicating very little difference, if any, between the two groups.

Belgium

Claeys-Thoreau et al. (1983) measured the blood lead levels of random samples in selected Belgian cities in 1979 and 1981. The 1979 sample consisted of 1678 people in 14 cities. The blood lead levels found in five representative cities for the adult population are presented in Table 13. Blood lead levels ranged from 15 to 24 µg/dL, with the highest value being found in Verviers where drinking water contains high concentrations of lead because of the widespread use of lead pipes. The table also shows the results for two

Table 13.

Levels of blood lead (µg/dL) in surveys in Belgium (Claeys-Thoreau, 1983).

Area	Year	Age Group	Both Sexes Median
Antwerp	1979	Adults	17.0
Brussels		"	18.0
Ghent		"	15.0
Liege		"	19.0
Verviers		"	24.0
Smelter Area	1981	Children	26.0
Verviers	"	"	19.5
Englis	1979	"	18.0
Beerse	"	"	14.0

groups of children living in two different exposure areas: a smelter area and the high-water-lead area of Verviers (n=415). These children were compared with children in two control localities (n=258). Median blood lead levels in the two control urban areas were 14 and 18 µg/dL, respectively, whereas in the two high-risk areas children had a much higher blood lead level, 26 µg/dL in the smelter area (not identified by name) and 19.5 µg/dL in the city of Verviers, higher than in the two control cities.

The importance of lead piping on body burden of lead was also shown in a contemporary study by Sartor and Rondia (1981). These authors collected blood samples from children attending the University Hospital and adult blood donors living in Liège (n = 859) and in Verviers (n = 568). Mean blood lead levels increased with age in Liège, with younger children (1-4) having slightly higher levels (Table 14). In Verviers, blood lead levels were found to be substantially higher and generally to increase with age. However, male children 5-8 years of age exhibited a high peak; a lesser peak was present in female children aged 9-14. Values as high as or higher than these were found in the adult population only in the age groups over 50.

Table 14.

Mean blood lead levels in groups exposed to lead piping and in an urban control group in Belgium (µg/dL) (Sartor and Ronida, 1981).

Age	Males		Females	
Groups	Liège	Verviers	Liège	Verviers
<1	10.7	-	8.7	-
1- 4	13.9	-	13.0	-
5- 8	13.7	34.9	12.5	21.3
9-14	17.2	23.0	12.6	26.4
20-29	19.3	24.2	12.9	19.4
30-39	19.1	28.2	15.3	-
40-49	21.2	28.4	16.8	24.9
50-59	20.4	33.2	16.0	29.4
60-69	19.9	33.5	16.9	32.3

France

Awad et al. (1981) surveyed eight large cities in France in June 1979. Venipunctures from 1877 subjects who were not occupationally exposed were analysed by atomic absorption spectrophotometry. The sample (Table 15) was subdivided into 10-year age groups: 0-10, 11-20, etc., up to 61-70. There were only three males and two females in the 0-10 age group, and 1 and 30, respectively, in the 11- to 20-year age group. Mean blood lead levels were higher for males, but conclusions about children were not possible because of the small sample.

Table 15.

Levels of blood lead (µg/dL) in surveys in France (Awad, 1981).

Area	Year	Age Group	Mean Males	Mean Females
8 large cities	1979	0-10	13.1	11.8
		11-20	12.1	8.6
		21-30	13.4	9.2
		31-40	15.3	10.7
		41-50	16.5	12.7
		51-60	16.2	12.7
		61-70	17.0	12.3
		70+	18.3	10.3

Malta

A survey was undertaken in Malta in June 1981, and January and July 1982 (Bruaux et al., 1983) (Table 16). Venipuncture samples were obtained from 70 subjects between 16 and 85 years of age. The sample had been selected for a survey on diabetes, and the opportunity was taken to analyse blood lead levels as well. A number of diabetics were discovered in the survey and were included in the analysis. Mean blood lead levels in Malta are very high: 45, 39.2, 37.5 µg/dL, respectively, in June 1981, and January and July 1982. Among the reasons for such high levels that had been proposed, the authors discussed the following:

- no large lead industry exists in Malta, nor are there regulations limiting lead in gasoline; part of the problem could be the emissions from motor vehicles
- regulations concerning the content of heavy metals in paints have existed only since 1981
- the dry and windy climate could possibly produce a higher exposure to lead dust
- lead in water has not been sufficiently tested to estimate its contribution to blood lead levels
- there is a need to measure heavy metals content in food and beverages.

Table 16.

Levels of blood lead (µg/dL) in surveys in Malta (Bruaux, 1983).

Area	Year	Age Group	Both Sexes (Mean)
Malta	June 1981	16-85	45.0
	Jan. 1982		39.2
	July 1982		37.5

United Kingdom

One of the few studies to report on temporal trends is that conducted by Elwood (1983) among women in Wales for the years 1972-1982. A stratified random sample was obtained for each year (Table 17). The results showed an substantial decrease in blood lead levels throughout the study period.

Blood lead levels of adults and children were measured in six major cities in 1979 (Royal Commission on Environmental Pollution, 1983); the protocol followed was prepared by the Commission of the European Communities. Comparisons were made between inner- and outer-city populations in six localities. The blood lead concentrations of all children sampled in the survey

Table 17.

Levels of blood lead (μg/dL) in surveys in the United Kingdom.

Area*		Year	Age Group	Both Sexes (Mean)
Wales		1972	Female	17.0**
		1974	adults	18.5**
		1977	"	14.0**
		1978	"	15.5**
		1980	"	9.0**
		1982	"	11.5**
Birmingham	I:	1979	Adults	13.6
	0:		both sexes	11.1***
Greater London	I:		"	12.0
	0:		"	10.2***
Leeds	I:		"	15.6
	0:		"	13.3***
Liverpool	I:		"	14.2
	0:		"	13.8***
Manchester	I:		"	17.0
	0:		"	16.6***
Sheffield	I:		"	14.6
	0:		"	13.2***

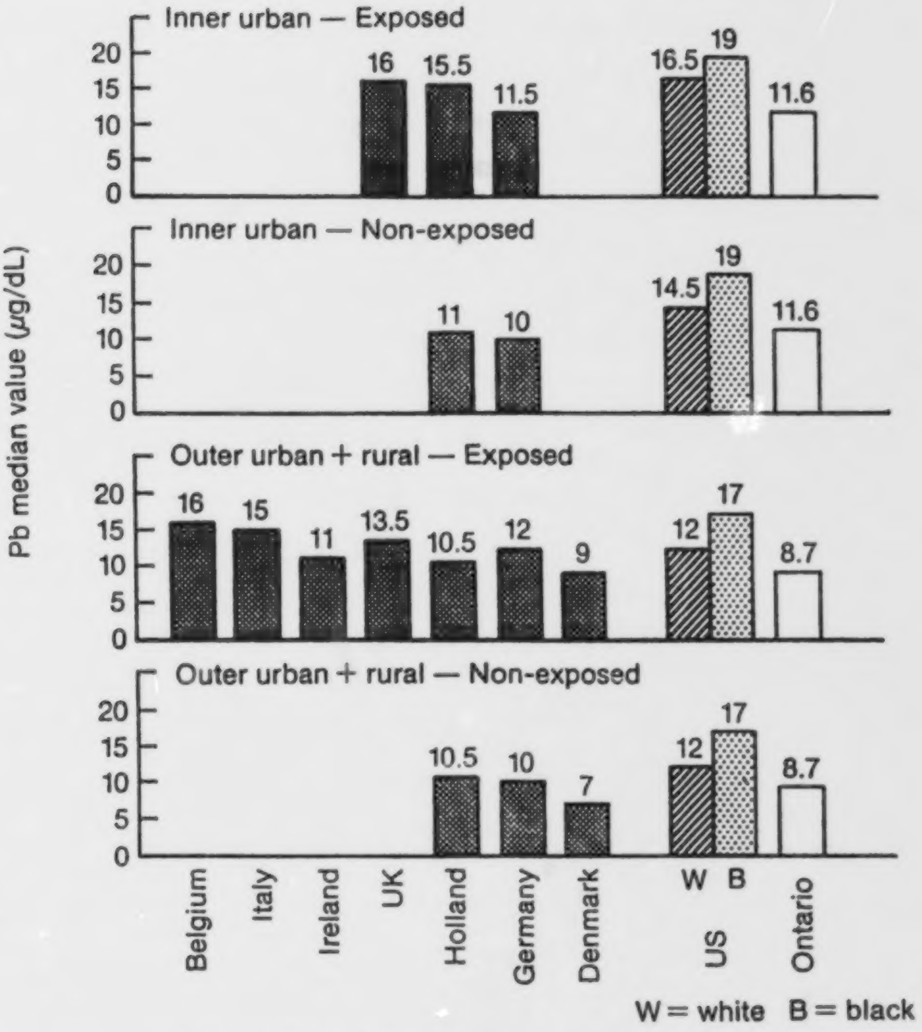
* I = inner city; 0 = outer city.
** Figures calculated from graphics.
***Geometric means.

ranged from about 5 μg/dL at age <1 year to a maximum of 18 μg/dL at age 3-4, declining gradually to around 14 μg/dL at age 10-12 years. The localities, however, were selected as being exposed to particular sources of lead (a goal peculiar to the European Community 1979 surveys), so that these levels cannot be extended to the general child population of the United Kingdom.

Shaper et al. (1982) measured PbB levels in men aged between 40 and 59 years in 24 British towns as part of the British Regional Heart Study. The authors were particularly interested in determining the influence of alcohol and smoking habits on blood lead levels. A group of 7378 (95% of 7735) "men randomly selected from age-sex registers of representative (medical) practices in 24 British towns" participated in the study. The blood lead levels were analysed by atomic absorption spectroscopy. The results showed that there is an increase in blood lead levels among smokers and drinkers. The authors did not report the mean blood lead levels in the various localities; however, the study is mentioned here to show the importance of taking into account smoking and drinking when assessing blood lead levels in populations.

Commission of the European Communities (CEC)

In the late 1970's, the Commission of the European Communities (CEC, 1981) sponsored a series of surveys to determine the extent of exposure to lead among the member states. Close to 18,000 subjects--8673 males and 8920 females, of whom 5800 were children--were surveyed in 168 separate areas and population groups. A common protocol was used, and the various working teams had a pooled quality control programme. In Figures 6 and 7 we have attempted to give a graphical impression of how the CEC survey results compare with those obtained in Canada and in the United States, whenever comparable data were available.



N.B. Ontario data are not separated between exposed and non-exposed. Canada Health Survey (Unseparated) median was 7 μg/dL.

Blood leads have been falling in many, if not all the countries. Data from different time periods should only be compared with caution.

Figures above columns are actual percentages.

Figure 6: Comparison of median blood lead values (μg/dL) among children of specified age groups in the following areas:

Sources: United States NHANES II (US), 6 mos - 5 yrs, 1976-80 (W-white, B-black)
Selected European Community countries, under 14 years, 1977
Canada Health Survey, 3-9 yrs, 1978-79
Ontario Blood Lead Survey, under 6 yrs, 1984.

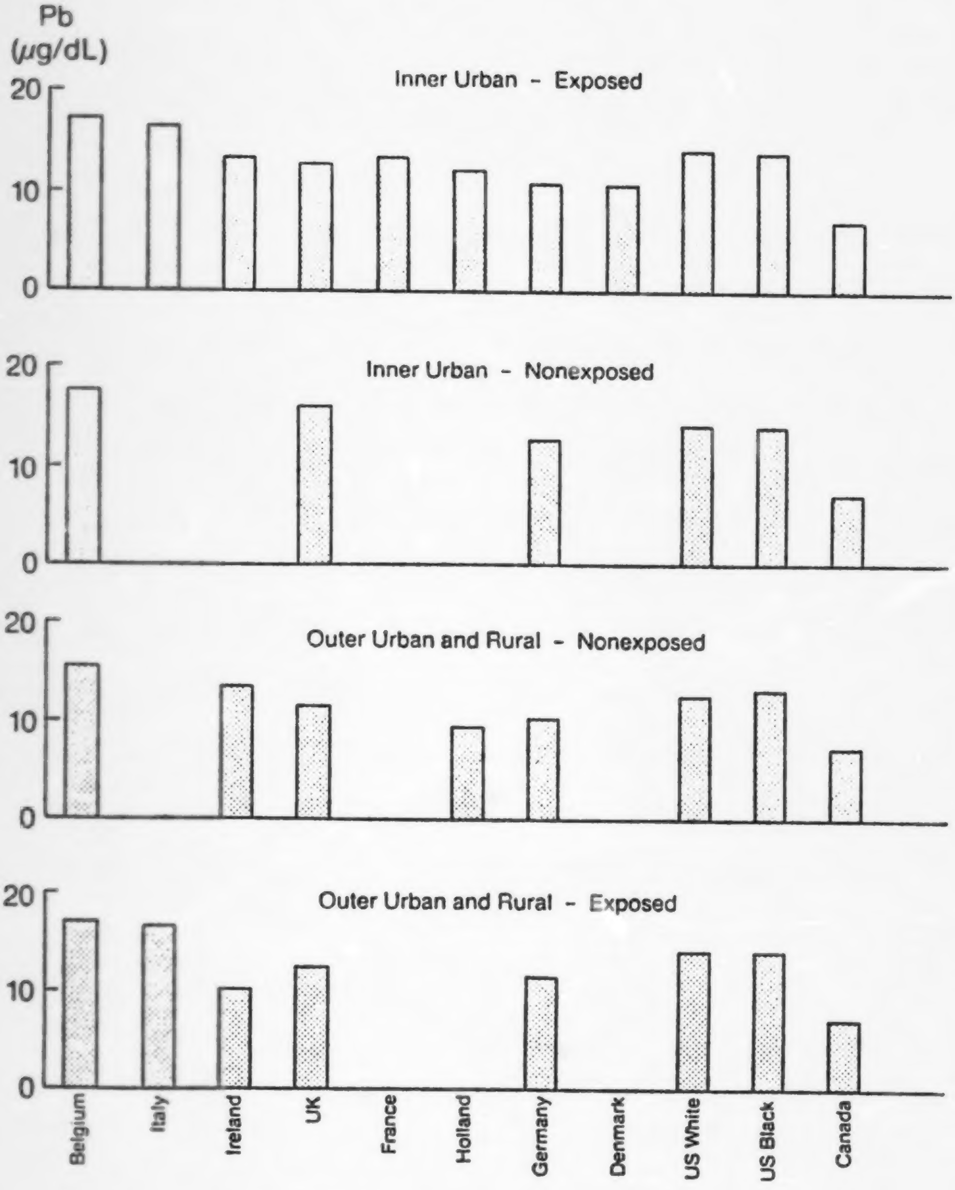


Figure 7 Comparison of specified average blood lead values among adults separated by location in the following areas:
United States NHANES II (US), 1976-80, geometric means
Selected European Community Countries, 1977, medians
Canada Health Survey, 1978-79, arithmetic means

Sources: CEC, 1981
Annest, 1983
Canada Health Survey, 1981.

Data from the European Communities are classified into four exposure categories by area: non-exposed inner urban, non-exposed outer urban and rural, exposed inner urban and exposed outer urban. Data from Canada and the United States are not subdivided in a comparable way, so the bars in the figures represent the best approximation to the data, based on published information.

The NHANES II classification distinguishes between central and non-central city areas with populations over one million and other urban areas, and rural areas under 2500, for the age groups 6 months to 5 years, 6-17 years of age and 18-74 (Table 18); the means are geometric. It is to be noted that data for blacks in non-central cities and rural areas are based on small numbers (62 and 69 adults and 56 and 81 children, respectively, for males and females). There is no clear pattern of similarity in blood lead levels between the central and non-central areas and between other urban and rural areas. To make the best approximation to the available European results, data in the graph compare central urban with the other three categories combined.

Table 18.

Geometric means (µg/dL) by age, race and residence, NHANES II 1976-80.

		Central Urban >1,000,000	Non-central Urban >1,000,000	Other Urban <2,500	Rural <2,500
Adults	White	14.1	13.9	12.9	12.3
	Black	14.0	15.5	12.3	15.1
Children 6m - 5y	White	16.3	15.3	14.4	11.8
	Black	21.6	18.5	19.2	16.5
Children 6 - 17y	White	13.6	14.4	11.4	10.5
	Black	14.3	19.2	13.6	13.0

Data on children for the European Community study (Figure 6) include all ages under 14. The best approximation to American data is for children under 17 years of age. Ontario data are for children under 6 years of age. Also, American and Canadian data are not available within the classification of exposure for localities used by the CEC. Although occupationally exposed individuals were not included in the European sample, American and Canadian data are not available within the classification of exposure used by the CEC. The same data have therefore been repeated for comparison with both exposed and non-exposed graphs. As to the data from the Canada Health Survey, the only geographical distribution possible is by region, so that data for all of Canada are presented for comparison purposes; they include all size communities (Figure 7). Only the urban and rural Ontario data are used.

Conclusions

The results from this review of average blood lead levels in various countries and in different centres seem to indicate that Canadians, children and adults, have blood lead levels lower than those found in most industrialized countries (see Figure 3), and it is only in close proximity to industrial emissions that levels apt to cause some concern have been found in children. Even in such circumstances, we seem to be better off than most industrialized countries.

Indeed, the results presented here are reassuring, particularly in that the number of children found to have levels higher than 20 μg/dL is small and has been decreasing with time. Such a decrease is not confined to Canada, but has been noted in most countries. The reasons for such a decrease are multiple and cannot be attributed solely to the reduction of lead content in gasoline.

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7. THE IMPORTANCE OF VARIOUS SOURCES OF LEAD

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Epidemiology is the making of measurements of clinical relevance and of known reproducibility in representative samples of subjects in defined communities. The principles of epidemiology have been well worked out and, in clinical fields generally and in cardiovascular disease in particular, the standard of most published work is very high. In environmental studies of lead, few epidemiological studies are of merit: often no attempt is made to study a representative sample, response rates often seem to be considered to be irrelevant provided numbers are large, measurements which are of doubtful relevance to human exposure are frequently made and often little attention is paid to confounding variables. Indeed, in some environmental studies blatant abuses of epidemiology occur (Elwood, 1984a). Some of these will be pointed out in the review which follows.

Changes in Blood Lead Levels

There is considerable interest in the well-documented fall in blood lead level in the United States since 1970. This has been attributed to a reduction of lead in gasoline on the basis of an association between changes in blood lead levels and changes in both gasoline lead sales and air lead concentrations (Billick et al., 1979; Rabinowitz and Needleman, 1982; Annest et al., 1983).

On the other hand, data from the United Kingdom suggest that a fall of about the same magnitude as in the United States (about 5% per year) has occurred in blood lead levels since about 1972. During the years 1971-82 inclusive, the total amount of lead added to gasoline in the United Kingdom (around 11,000 t/a) varied by only about ±5% (Department of Transport, 1979; Royal Commission on Environmental Pollution, 1983). More recent figures are not yet available and, although the concentration of lead in gasoline is being reduced in the United Kingdom (most recently the concentration is 0.37 g/L compared with 0.4 g/L in 1981), sales of gasoline were increasing up to 1982 (Royal Commission on Environmental Pollution, 1983) and have probably continued to do so.

Evidence of a fall in blood lead levels in the United Kingdom comes from a number of sources. The Department of the Environment (1981) described a fall of about 5% per year between two series of surveys throughout the United Kingdom in 1979 and 1981. The earlier of these surveys had been based on random samples of defined communities, but in 1981 an attempt was made to survey communities in areas of possible lead pollution. It could therefore be argued that a true fall in blood lead level was underestimated by a comparison of these two series of surveys. A report based on male subjects presented for pre-employment medical examinations in the United Kingdom also suggested a fall during the 1970's of about 18% (Oxley, 1982). Three surveys in Wales have also suggested a fall of about 5% per year since about 1970. One of these (Elwood, 1983a) was based on changes in 10 surveys of random population samples conducted between 1972 and 1982. Another involved a comparison of lead levels in blood samples taken in 1969 and stored at low temperature with fresh samples taken from the same subjects in 1982 (Elwood, 1983b). A third study compared blood lead levels in the same subjects in two minor urban and several very rural areas in north-east Wales in 1976, 1981 and 1984 (Elwood and Toothill, 1985). Finally, a report from New Zealand, where there has as yet been no change in lead in gasoline, described a fall of about 4% per year both in unexposed 'normal' subjects and in subjects examined in pre-employment examinations between 1974 and 1984 (Malpress et al., 1984). Although these subjects are not representative of the general population of New Zealand, the report stated that the criteria for selection for testing for lead were unchanged during the period of the study.

None of these studies had been set up specifically to examine changes in blood lead levels, and all can be faulted, both those in the United States and those in the United Kingdom and New Zealand. However, the results are remarkably similar in the different countries. This suggests that there have probably been important changes in environmental lead levels in a number of sources, and studies which attempt to link the changes within a country to a single environmental source are naive.

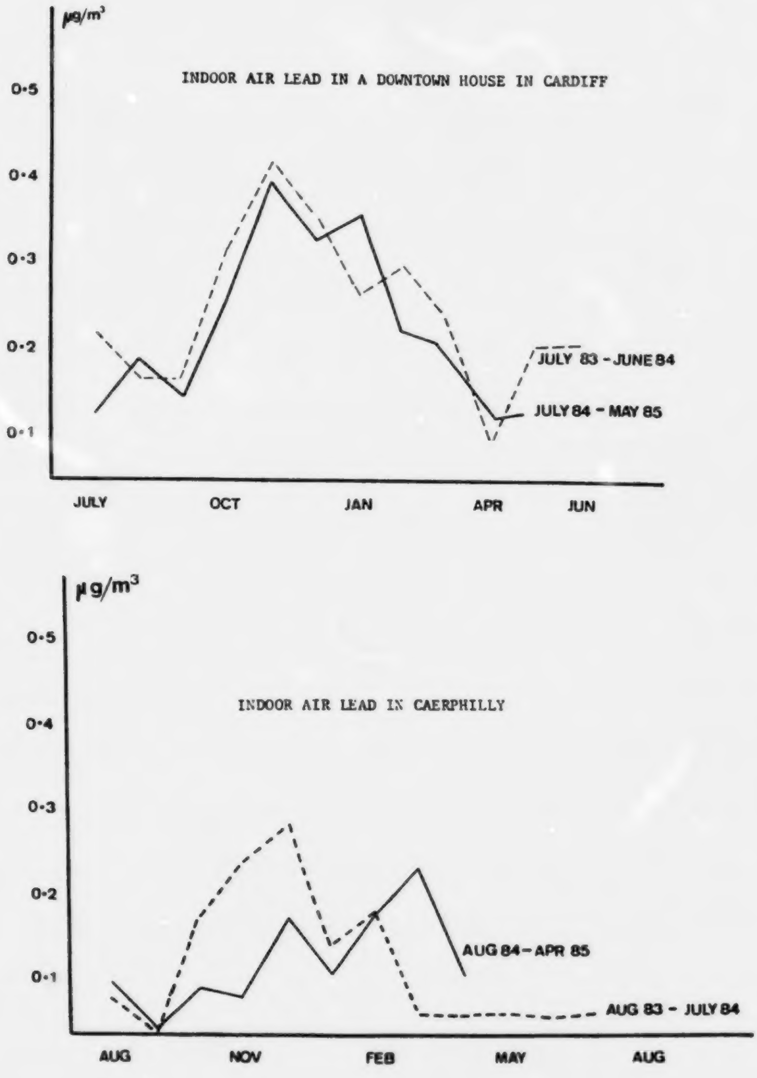
The intention in this paper is therefore to review some of the evidence on the clinical importance of lead in each environmental source, commenting where possible on changes in levels over time.

Lead in Air

The relationship between air lead and blood lead level has proved to be elusive, and serious difficulties arise from several sources. Firstly, the importance of non-inhalation routes of air lead to blood is not known. Secondly, the measurement of air lead levels in a way relevant to the actual exposure of subjects is difficult. However, perhaps the most obvious limitation in the available evidence is that much of it comes from studies which have been based on subjects exposed to very high air lead levels around lead smelters (Yankel et al., 1977; Angle and McIntire, 1979; Roels et al.,

1980) subjects exposed to very high levels, such as cab drivers (Azar et al., 1973) or experimental subjects (Chamberlain et al., 1975). The relationship between air and blood lead level is almost certainly curvilinear (Hammond et al., 1981), and it is clearly hazardous to extrapolate back from subjects exposed to very high air lead levels. Snee (1982) showed that such extrapolation can lead to overestimates of the contribution from air with less than 1 or 2 μg/m^3 Pb, and yet the levels relevant to most communities are certainly very much less than this (see Figure 1). It is therefore difficult to judge

Figure 1. Urban and Rural Indoor Air Lead in Wales



the relevance to the general community of the studies by, for example, Yankel et al. (1977), who described air lead levels of up to 17 μg/m^3, or Azar et al. (1973), with levels up to 6 μg/m^3.

Even in studies in the general community, ambient air lead levels, as conventionally measured, probably only remotely represent the true air lead exposure of subjects. In part this arises from the fact that air lead is traditionally measured at an elevated, and often remote, site out of doors; although indoor air lead levels are much lower (Tosteson et al., 1982), there is probably a variable ratio between outdoor and indoor measurements depending on factors in the dwelling (Elwood, 1984b). Unfortunately, only a few studies have attempted to measure air lead exposure realistically, either indoors (Rabinowitz et al., 1984; Elwood et al., 1984) or by personal monitors (Azar et al., 1973).

It has been further suggested that air lead exposure within motor vehicles may be highly relevant, and markedly elevated levels have been found inside vehicles (Chamberlain, 1985). There are very few relevant epidemiological data, but the point is of particular interest in the evaluation of gasoline lead as a contributor to blood lead. For example, in the NHANES II study, a 6 μg/dL fall in blood lead level can hardly be attributed to overall changes which appear to have taken place in ambient air lead level in the United States from 0.72 to 0.24 μg/m^3 (CFR, 1982a, b).

Elwood et al. (1977) examined the association between car ownership and blood lead level in a survey in Manchester and found that in one out of four groups of children and their mothers there was a 13% excess in blood lead levels in children whose families owned a car. In two of our own surveys of adult women, one in a downtown area in Swansea, South Wales, the other in a rural area in North Wales, we failed to find any evidence of an association between car ownership, or time spent travelling in a car, and blood lead levels (see Table 1). The relevance of this exposure is therefore very doubtful.

Table 1.

Blood lead levels (μg/dL) in random samples of women in an urban area and in a rural area subdivided by time spent travelling in a car.*

	Blood Lead Levels		
Hours Per Week in a Car	n	Mean	SD
Urban area			
None	27	18.0	7.2
< 2	32	14.9	7.2
2 or more	21	16.6	8.1
Rural area			
None	14	12.6	5.1
1-3	77	10.5	3.9
4-6	43	9.0	3.2
7-9	11	10.6	3.5
10+	26	12.7	6.8

* In both areas, means are homogeneous at $p < 0.05$.

Undoubtedly, however, the main uncertainties in the evaluation of air as a source of blood lead relate to the importance of fallout lead from air in dust and on food.

An attempt to quantify non-inhaled lead from gasoline was made in the Isotopic Lead Experiment in Turin (Facchetti and Geiss, 1982). In this study it was estimated that inhaled lead accounted for only 8-54% of the total contribution from gasoline (EPA, 1983). However, there are so many uncertainties in this work that the results cannot be accepted with confidence. The sample examined is tiny and unrepresentative, the levels of blood lead were highest in the most rural areas, and it is in these that the largest contribution of lead from gasoline by non-inhaled routes (3.2 µg/dL blood) appears to have occurred. Furthermore, the estimates are based on an assumed inhaled air-blood lead relationship.

Wijn et al. (1983) examined one aspect of this problem of non-inhaled air lead. They showed that vegetables grown alongside busy highways had two to three times the lead content of vegetables which had been grown well away from traffic. At the same time they were unable to detect any elevation in the blood lead levels of subjects who had had a high consumption of these contaminated vegetables. Chamberlain (1983) examined this same problem of fallout of airborne lead onto crops. He pointed out that although foliage near motorways can show heavy contamination, translocation to inner leaves, tubers, fruit and seeds is very slight. He went on to measure ^{210}Pb in fallout and in the total diet, and estimated that lead from air contributes about 13 µg/day to the average adult diet in the United Kingdom. However, this last may well be an overestimate as it ignores the ^{210}Pb obtained by routes other than fallout.

Ter Haar (1970) also examined crops adjacent to a busy highway and in greenhouses some distance away. Differences in lead levels were very small for 10 vegetables, and from this he estimated that airborne lead could contribute only a few per cent of the lead in the average United States diet even if all the crops had been grown in areas near busy highways.

However, it is probably hand-to-mouth activity in young children which is likely to be one of the most important routes for non-inhaled air lead. Gallacher et al. (1984b) examined this in a sample of 1- to 3-year old children living alongside busy main roads in South Wales industrial valleys and in culs-de-sac off these main roads. They found no significant difference in the distributions of the lead concentration in dust samples taken from the sidewalks outside the houses (95% ranges 172-731 μg/g and 83-870 μg/g outside 42 and 28 homes, respectively), although there was a larger total amount of lead per unit area along the heavily travelled roads. However, they found only trivial differences in the amount of lead removed by a 'wet wipe' from the hands of the children living along the main roads and from the hands of children living in the culs-de-sac with no traffic.

EPA (1983), having reviewed all the evidence, judged that the air-blood lead relationship was probably about 1.64 μg/dL blood per 1 μg/m^3 air in adults and 1.96 in children (at 1-2 μg/m^3). These estimates imply that air is likely to be a very small contributor to blood as air lead levels, even in most urban areas, are probably well below 1 μg/m^3 (see Figure 1). However, uncertainty remains about the importance of non-inhalation pathways for air lead. One of the studies drawn on by EPA (1983) was the Omaha lead smelter study (Angle and McIntire, 1979). Angle et al. (1984) re-examined these data and recommended a linear model for air-blood lead. They further commented that because soil and dust lead are correlated with air lead around the smelter, the increase in total exposure, via inhaled and non-inhaled routes, represents an increase of 4-5 μg/dL as lead in air increases by 1 μg/m^3. Again, however, as these estimates are derived from a heavily contaminated area, the recommended slope and the suggestion that it is linear must be viewed with great caution. At the same time, even if it is accepted, a slope of 4-5 implies that, in downtown Cardiff (see Figure 1) less than 1.5 μg/dL lead in blood can be attributed to airborne lead via all possible routes.

Lead in Soil

Lead is a normal trace element in rocks and soils, but soil is a major sink for anthropogenic lead, and contamination from industry, coal ash, paint, sewage sludge, mining and smelting as well as fallout from airborne gasoline lead have led to general soil pollution. Apart from sites heavily contaminated by industry or mining, urban areas in the United Kingdom have mean surface soil lead levels around about 100-400 µg/g, with an individual range from perhaps 40 to 2000 µg/g. In some areas, however, levels are much higher, with a mean in one city of 780 µg/g and 15% of samples over 1000 µg/g (Davies et al., 1979). Levels in cities in the United States are probably not very different: Mielke et al. (1983) reported that 10% of soil samples from vegetable gardens within a radius of 30 miles of an urban centre had levels exceeding 780 µg/g. In areas around a lead smelter or areas contaminated by lead mining, these levels may of course be grossly exceeded.

One possible pathway from soil to blood is through vegetables. Gallacher et al. (1984a) examined this in an area very heavily contaminated by lead mining spoil. They found that the contribution to blood of lead from locally grown vegetables was up to about 3 µg/dL in those who consumed much local produce, but other pathways from soil appeared to contribute about the same amount to blood.

It is unfortunate, however, that most studies of the relationships between soil and blood lead have been based on populations exposed to very high levels of soil lead, either in areas around a lead smelter (Yankel et al., 1977; Schmitt et al., 1978; Angle and McIntire, 1979; McMichael et al., 1985) or in areas around old lead mines (Gallacher et al., 1984b). Extrapolations from the results of such studies to the general community are hazardous. In any case, pathways from soil to blood are complex, and their importance must vary enormously between children and adults, and in different situations. It is not surprising, therefore, that in many studies no significant relationship between soil and blood lead was detected, and in those in which it has been, the estimates of the relationship have varied enormously. EPA (1983) summarized a number of studies giving estimates from 0.6 to 7.6 μg/dL blood per 1000 μg/g soil. In our own work based on a community in an area heavily contaminated by lead spoil (Gallacher et al., 1984a, b), the increase per 1000 μg/g of soil is about 2 μg/dL in adults and 4 μg/dL in children.

Lead in Dust

Levels of lead in household dust appear to be higher in the United States than in the United Kingdom, although comparisons are difficult to make because of differences in sampling procedures. Baker et al. (1977) refered to a mean level of 718 μg/g, Landrigan et al. (1975) to means of 816 and 922 μg/g, Solomon and Hartford (1976) to a mean of 600 μg/g, and Stark et al. (1982) to a range of mean levels up to 630 μg/g. On the other hand, Angle and McIntire (1977) referred to somewhat lower levels, with a mean of 337 μg/g in 1074 samples taken in three areas, one of which was adjacent to a lead smelter. In general, surveys in the United Kingdom seem to yield lower levels. For example, the surveys of Davies and his colleagues in Wales (Davies et al., 1985) are probably the most extensive, and these describe levels with means of about 200 μg/g.

This probable difference in the distribution of lead levels in house dust in the United States and in the United Kingdom is almost certainly a reflection of the frequency of use in the past of lead-based paints in the United States. References to leaded paints are rare in reports from the United

Kingdom, but frequent in papers from the United States. Lin-Fu (1982) referred to a survey in the United States in 1978 which indicated that over half the homes in the United States (over 49 million dwellings) were built before 1960 and may have lead paint. Tyler (1970) reported that 67% of samples taken from 5466 homes in Philadelphia showed over 1% lead. Landrigan et al. (1975) found paint with over 1% of lead in 25-35% of homes. Lin-Fu (1980) also expressed the belief that lead-based paint on millions of homes in the United States "remains the single most important high dose source of lead in children living in poorly maintained homes". It seems to be widely agreed that leaded paint is probably the most frequent source in severe pediatric cases of lead toxicity (Barltrop, 1968; Barltrop et al., 1975; Mahaffey, 1983). However, paint has been questioned as an important source of mild to moderate lead toxicity, although the logic of this claim is somewhat obscure, and Lin-Fu (1980) referred to a series of children with raised blood lead levels (40-70 µg/dL) in the homes of whom high lead levels in peeling paint were found in half, compared with one-quarter, of the homes of a control group with lead levels below 30 µg/dL.

The frequency with which leaded paints seem to have been used in the United States is alarming, and their effects may be even more widespread than these reports might suggest. Vostal et al. (1974) found median lead concentrations approximately five times higher on the interiors of inner-city houses than those found in suburban homes in Rochester, N.Y. Sayre et al. (1974) also commented on this finding, but went on to point out that as the lead on interior surfaces can be rubbed off with a moist towel, contamination of the hands of children may readily occur. Hammond (p. 27) describes how, in a study of the homes of 285 children in Cincinnati, almost half the variance in house dust lead levels can be attributed to the lead levels in paint and in surface soil (itself a reflection of exterior lead paint).

The origin of the lead in dust in homes in which leaded paint has not been found is uncertain. Undoubtedly there are numerous extrinsic and intrinsic sources. In an area of old lead mining with very heavy soil contamination, Davies et al. (1985) found a correlation of r = 0.5 between the soil lead outside and dust lead inside houses. Other studies around lead smelters have given similar correlations: r = 0.4 in Diemel et al. (1981), 0.2 in Yankel et al. (1977) and 0.3 in Angle and McIntire (1979). However, these data all relate to very heavily contaminated areas, and so extrapolation to general housing could be quite misleading. Yet data from more usual areas of housing seem to be uncommon in the literature. In a typical urban area in Wales, we found a correlation of only r = 0.10 between house dust lead and lead in dust on the sidewalk outside of 100 houses which were right on the sidewalk with no gardens.

In fact, there are a number of reasons why it seems likely that intrinsic sources are the most important contributors to house dust lead. Firstly, it has been shown in a number of studies that blood lead levels correlate with the age of their dwelling (Department of the Environment, 1981; Harvey, 1984; McBride, 1984). Then in Wales, where we have no reason to believe that leaded paint is a common source of lead, dust samples have been taken in surveys of many hundreds of homes and we have been impressed by the relatively similar means and distributions found in many different kinds of areas. For example, in an industrial town with an elevated motorway the geometric mean was 258 (95% range 62-1074 µg/g), and in a remote rural village 177 (36-874 µg/g). Six other areas in which the homes of random samples of subjects were examined lay between these extremes. It was only when we went to remote unacculturated islands off the coast of Ireland that we obtained really low levels. For example, on Tory, 7 miles north of the Irish coast, and on Aran Island, 20 miles off the west coast of Ireland, the means were 36 and 41 (95% range 6-231 μg/g and 9-178 μg/g). These islands are trafficless, yet on another trafficless island, Sark C.I., where the manner of life is probably similar to that of Wales, we found levels indistinguishable from the mainland (geometric mean 204, range 53-773 μg/g) (Elwood et al., 1985). On the other hand, the range within each area is very large, and apart from Tory and Aran Island, both the means and ranges are remarkably similar, suggesting that the sources of lead within a home are numerous, and lead from outside, including airborne fallout from gasoline lead, is unlikely to be a major contributor.

An important advance in the evaluation of dust lead was made by Sayre et al. (1974), who measured lead on hands by a 'wet wipe' method. Using this method, Charney et al. (1980) showed a significant relationship with blood lead in children. Gallacher et al. (1984b) also showed that both women and children in an old lead mining area had significantly higher hand lead levels than women and children in a similar control area, and found that in a regression analysis of lead in a number of environmental sources 'hand lead' was the major predictor of blood lead in children ('r' = 0.5, $p < 0.01$), although there was no significant association in women. Charney et al. (1983) took this method of evaluation of dust lead further in a controlled trial of dust control in the reduction of blood lead in young children. Although this trial would satisfy few of the rules for a clinical randomized controlled trial, it did suggest some benefit from dust control, albeit limited to those with the highest blood lead levels.

In relation to lead in gasoline as a possible source of blood lead via the dust-hand-mouth route, it is of interest that Gallacher et al. (1984b) found no evidence of differences in hand lead in 1- to 3-year-old children (or their mothers) living in roadside dwellings on busy roads (mean 15.1 µg) and in children living in a village remote from industry and heavy traffic (mean 14.1 µg).

Studies of the association between house dust lead and blood lead levels have given very inconsistent results, and in general the only studies in which a statistically significant association has been found are those around lead smelters where levels are enormously high. For example, Landrigan et al. (1975) found a highly significant relationship between blood and dust lead levels in an area with a mean dust lead level of 4022 µg/g but not in two areas with means of 922 and 816 µg/g. EPA (1983) presented a summary of studies and, although they judge the overall relationship to be equivalent to 1.8 µg/dL lead in blood per 1000 µg/g lead in dust, the data from the different studies show very little consistency, yielding slopes ranging from well below 1 to over 7. Duggan (1980) also reviewed the available evidence and concluded that a slope of 5 µg/dL per 1000 µg/g dust lead is reasonable; however, in view of all the uncertainties and the fact that these estimates lean heavily on studies of children exposed to enormously high levels, such as near a lead smelter, one doubts their credibility.

In fact, several alternative approaches to the evaluation of dust as a source of blood lead have given unpromising results. Chamberlain et al. (1978) pointed out that many surveys of children and their mothers show, fairly consistently, child:mother ratios around 1.3. Male:female ratios in adults, however, are higher than 1.3, so the ratios in children are intermediate to those between their parents. This is inconsistent with the existence of an important pathway in children and not in adults. Ter Haar and Aronow (1979) used a novel approach. They used estimates of the naturally occurring isotope ^{210}Pb excreted by children to determine the relative amounts of dust (in which the level is high) and lead paint (in which the level is low). Despite large differences in faecal lead in a group of children with lead poisoning and a control group, there was no difference in ^{210}Pb excretion. The authors claimed that these results provide 'sound' evidence that suspended particulate lead in dust or air could not have been the cause of the lead poisoning. On the other hand, Stark et al. (1982) inferred that soil, paint and house dust lead are of little importance because they could only 'explain' 12% of the variation in the blood lead in their sample of 377 children aged 1-6 years. However, this conclusion is unreasonable, because the actual exposure of subjects to lead in dust is probably only very poorly reflected in the estimates of dust lead which are usually made in a community-based study.

It is unfortunate that more is not known with reasonable certainty about dust as a source of lead. Of all the sources of lead it is with house dust lead that the most important confounding relationships with other factors are likely to occur. The highest levels of dust lead will occur in poor, badly maintained homes in the least privileged parts of our cities (Stark et al., 1982) where lead levels in other environmental sources are likely to be at their highest. Furthermore, children residing in such areas are likely to have undesirable levels of all psychosocial factors which are relevant to blood lead levels, such as the standard of caretaking (Hunt et al., 1982) and other aspects of psychosocial adaptation (Singhi et al., 1981).

Lead in Food

It is frequently judged that the main exposure to lead is in the diet (e.g. Sherlock et al., 1983). Estimation of lead in the diet is, however, one of the most difficult techniques in this field of research. There are a number of methods, including the summation of estimations of the lead content of foodstuffs in 'diary' or 'market basket' records, the analysis of lead in simulated diets and the analysis of duplicate diets collected from subjects in the community (Department of the Environment, 1982). A small amount of comparative work has been done on these different methods, and it is not very reassuring. For example, a comparison of "diary" estimates and analyses of duplicate diets all collected in a single village in the United Kingdom gave mean estimates of 110 and 69 µg/day (Sherlock et al. 1983).

In fact, there are so many uncertainties relevant to the contribution of food to blood lead that reliable overall evaluation is probably impossible. Thus, vegetables absorb lead from water during cooking, and the amount absorbed from soft water is greater than that from hard water (Little et al., 1981). The composition of a meal also affects lead absorption; although 40-50% of a radioactively labelled lead marker was absorbed when taken alone in water, this fell to 14-19% with beverages and 3-7% with meat or vegetables (Heard et al., 1983).

With regard to changes in lead levels in food during recent years, one can probably be more confident. Not only has lead in canned foods fallen to perhaps one-tenth of the levels present in the old soldered and lacquered cans, but canned foods have given place very largely to fresh and frozen foods. Furthermore, in the United Kingdom lead levels in most individual foodstuffs have fallen to one-half or less of the levels prior to about 1970

(MAFF, 1982). This has led to a decrease in the lead content found on analysis of simulated diets in the United Kingdom from about 120 µg/day in 1975 to about 80 µg/day in 1981 (MAFF, 1982). Similar estimates come from Denmark, where there is evidence of a fall in lead in cereals since about 1962 and a substantial fall in total dietary lead from about 160 in 1962 to about 90 µg/kg (fresh weight) in 1976 (Solgaard et al., 1979).

Particular interest can be taken in alcoholic drinks, as many studies have shown a significant association between the intake of these and blood lead levels ('r' = 0.32 in Moreau et al., 1982, and 0.12-0.30 in Grandjean et al., 1981). A further aspect of the potential importance of alcohol arises from its frequent confounding relationship with cigarette smoking, and Shaper et al. (1982) have shown that men who smoke (20 or more cigarettes per day) and drink (six or more drinks per day) have blood lead levels which are, on average, about 44% higher than those in men who neither smoke nor drink. The prevalence of heavy smoking has fallen in recent years in many countries, and the lead content of alcoholic drinks has also probably fallen. In the United Kingdom, analyses of beer, cider and wine made prior to 1966 suggested levels of 0.2-1.8 µg/g whereas in 1980 levels were substantially lower (MAFF, 1982).

It seems reasonable, therefore, to assume that the lead content of an average diet has fallen substantially during recent years, although confident estimates of the size of the fall cannot be made. It is difficult, therefore, to accept as reasonable the dismissal by the NHANES II team of changes in food lead levels as a contributory cause of changes in blood lead levels in the United States between 1975 and 1980. In any case, the data for food lead levels in the United States which have been quoted to justify this dismissal (ICF, 1982), suggesting increases in the dietary lead intakes during the period of NHANES II of 23-76%, are somewhat incredible.

Lead in Water

Water has probably been more closely investigated in the United Kingdom as a source of blood lead than any other source. A survey throughout Great Britain showed that 10% of dwellings have over 10 μg lead per litre of tap water, and in over 4% of homes the level is over 100 μg/L (Department of the Environment, 1977).

Little interest seems to have been taken in water lead levels in the United States, although high levels have been shown to occur in some areas. For example, Worth et al. (1981) found 'first draw' water lead levels from 13 to 1108 μg/L and 'running' water levels of 13-208 μg/L in Boston. Karalekas et al. (1983) also reported that the mean water lead levels in selected homes in Boston were about 82 μg/L, with a total range from less than 0.05 to 960 μg/L. After 1977, when anticorrosion water treatment was introduced, the mean water lead level in 23 selected houses was about 33 μg/L, with a range up to 900 μg/L.

At the same time it must be noted that the usual methods of measurement of water lead give estimates which are probably somewhat remote from the actual intakes of subjects. In the United Kingdom water lead is usually estimated on a 'first flush' sample taken from the cold kitchen tap, and this correlates fairly well with the blood lead levels of residents (Moore et al., 1977; Thomas et al., 1979). Prolonged flushing of a tap before a sample is taken can reduce the lead content of tap water to almost zero (Thomas et al., 1981). Wong and Berranc (1976), who also examined this point, showed that the lead levels in water taken from a tap fall from about 240 μg/L in the first litre of 'first flush' water to 17 μg/L in the second litre of water. It is therefore not surprising that the study of Rabinowitz et al. (1984) of infants born in Boston failed to detect any association between cord blood lead and water lead level estimates on samples taken after flushing for 1 min, and these authors may have overestimated the contribution to blood lead of lead in the other sources they measured because water lead was measured in a way which may have been unrealistic. One wonders in how many other studies water has been dismissed as an unimportant source of lead on the basis of an unrealistic sampling procedure (Thomas and Elwood, 1976).

Water lead may be of particular importance for several reasons. Firstly, levels can be high and variation from dwelling to dwelling large (Department of the Environment, 1977; Thomas et al., 1979; Sherlock et al., 1982), even in areas in which there is a non-plumbo-solvent water (Pocock et al., 1983; Elwood et al., 1984). Furthermore, in an area in which the water supply is hard, relatively high water lead levels can occur (Thomas et al., 1981). Secondly, absorption of lead from water is probably high. Heard et al. (1983) found that volunteers absorbed 40-50% of a radioactive lead marker added to water, and to this must be added lead absorbed onto vegetables during cooking (Little et al., 1981). Smart et al. (1981) estimated that water, both directly and indirectly through absorption onto vegetables, contributes at least 10% of dietary lead. We estimated that in areas with quite low water lead levels in Wales (means between about 4 and 21 μg/L), water lead explained 23% of the variance in blood lead (Elwood et al., 1984). Differences between areas are probably considerable, however, and Pocock et al. (1983) estimated that only about 7% of blood lead in men in English towns with no plumbo-solvency problem was derived from water.

The third reason why water lead is important is because high levels occur most frequently in old properties and in less privileged areas such as 'downtown' urban areas. This enables other environmental factors such as air lead to confound the effects of water lead and a consequent overestimation of the importance of lead if only certain sources are examined. Confounding effects of lead in water are seldom considered, and water is either ignored (Roels et al., 1980) or dismissed as a significant source of lead because levels were found to be "generally low" or "within established standards" (Yankel et al., 1977). Although water may be a relatively minor source in subjects exposed to very high levels from other sources, it is bound to become of relatively greater importance if other sources have low levels; as higher water lead levels are likely to be associated with older housing in inner-city areas with higher dust and air lead levels, the potential for bias if water is ignored may be considerable.

The confounding effects of water lead on the association between blood lead and air lead levels in areas of modest environmental levels can be illustrated by data from surveys of women in Wales (Elwood et al., 1984). The slope of the blood lead - air lead regression, with no other factor considered, was 2.4--that is, an increase in air lead of 1 $\mu g/m^3$ was associated with an increase in blood lead of 2.4 µg/dL, and the proportion of the total variance in blood lead 'explained' by air lead was 19%. When house dust level and social class were added to the regression, the slope declined to 2.2, and the proportion of the variance in blood lead 'explained' increased to 20%. When water lead levels were added, the slope fell to 1.8, and the variance 'explained' increased to 38%. No area with a plumbo-solvent water supply had been included in this study, and all the water lead levels were low. It may be, therefore, as suggested by Pocock et al. (1983), that at the low levels of environmental lead which generally occur, water is a more important determinant of blood lead than is generally realized, and is a most important confounding factor if ignored.

One of the first studies to examine the quantitative relationship between water and blood lead levels in a representative population sample fitted a linear model (Elwood et al., 1976). However, at an early stage it was suggested that the relationship could best be described by a cube root regression (Moore et al., 1977). Whereas such a relationship described the situation well in areas with very high water lead levels, the use of such a relationship as a basis for extrapolations is probably undesirable because the slope approaches infinity at low water lead levels.

Having reviewed all the available evidence, the EPA (1983), preferring a linear model, chose that described by Pocock et al. (1983). This gives a slope of 0.06 µg/100 dL lead in blood for every 1 µg/L lead in water, and this is very close to that which we obtain in Wales (approx. 0.05). Such a slope implies that a substantial contribution (up to about 3 µg/dL lead in blood) can be contributed by water which is below the standards recommended by the European Commission (50 µg/L) and EPA (50 µg/L). It is not surprising, therefore, that in a study in Wales based on adult women, who can reasonably be assumed to reflect environmental lead levels in the home better than men, water was found to be the most important source of lead, 'explaining' about 23% of the variance in blood lead levels (Elwood et al., 1984).

Conclusions

The determinants of blood lead levels are lead in air, soil, dust, food and water. The evaluation of the relative importance of these environmental sources is impossible given the present evidence. The degree to which current methods of measurement of lead in the sources truly represent the actual exposure of subjects is unknown. This is especially true of air, soil, dust and water. On the other hand, although measurements of food lead closely represent exposure, the measurements of lead are technically very difficult to make, and the collection of adequate dietary material from a representative population sample would be a formidable undertaking.

Many studies have attempted to evaluate the different sources in terms of the proportions of the variance in the blood lead levels of a group of subjects which are 'explained' statistically by the levels of lead in the various sources. The validity of such estimates depends, among other things, on the relevance of the environmental measurement to the true exposures of the subjects, and on the degree to which that environmental source can be assumed to be independent of all other sources. This last is of particular importance in studies based on communities living in inner-city areas or around a lead smelter.

These difficulties aside, it is clearly hazardous to extrapolate conclusions derived from a study of subjects in one area to other communities in which the balance between the various environmental sources may be quite different. Studies based on lead smelters or other special situations raise special difficulties in this context, but extrapolation of conclusions is also invalid for any study based on selected subjects, rather than a random sample of residents within a defined area.

Attempts to evaluate the contribution to blood lead of a particular source have been based on changes over time of lead in the source and in the blood of exposed subjects. Results from such studies are probably uninterpretable. The levels of lead in all environmental sources undoubtedly change over time, and for almost all sources these changes have been very inadequately recorded.

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8. HUMAN EXPOSURE TO LEAD FROM GASOLINE*

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Individuals are exposed to lead from gasoline through many pathways. When leaded gasoline is burned in an engine, small amounts are deposited in the engine and exhaust system, but most of it is emitted from the tail pipe to the air where it remains suspended for a time before settling to the ground. Some exposure occurs through direct inhalation of the emitted lead. Additional exposure occurs from ingestion of lead-contaminated dust or inhalation of such dust that has been stirred up. Lead from gasoline also deposits on food crops and is then ingested. These multiple routes make it very difficult to model individual exposure pathways. It is possible, however, to estimate the total amount of lead exposure from gasoline using statistical methods, as discussed below.

Recent Studies

Several recent articles have shown that blood lead levels for all groups will fall as gasoline lead content falls. The first important statistical studies were done by Billick et al. (1979) who showed a strong relationship between the blood lead levels of several hundred thousand children screened in New York City's lead screening programme and local gasoline lead use. Figure 1 shows this relationship graphically.

In 1982, Billick presented additional regression analyses on data from

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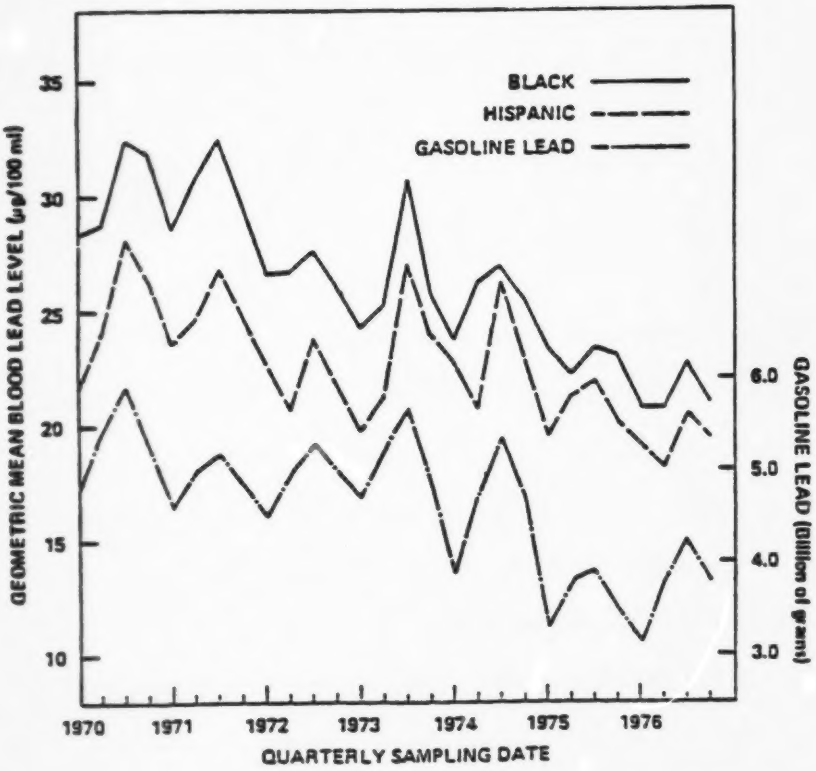
New York City's lead screening programme (with data on several additional years), a Chicago screening programme (800,000 children older than 10 years of age) and a Louisville, Kentucky, programme, all of which confirmed the earlier results.

A report prepared for the US Environmental Protection Agency (EPA) (Janney, 1982) found a strong association between gasoline lead and blood lead in the data from the second US National Health and Nutrition Examination Survey (NHANES II), after controlling for age, race, sex, degree of urbanization and income. Analyses of the NHANES II data by the US Centers for Disease

Figure 1 Relationship between Gasoline Lead and Blood Lead in New York City



Control (CDC) and the US National Center for Health Statistics performed concurrently showed similar results.

Annest et al. (1983) published a paper analysing the nation-wide downward trend of blood lead levels from 1976 to 1980 that was demonstrated in the NHANES II data. Blind quality control data were used to ensure that there was no drift in laboratory measurements. This downward trend was present after controlling for age, race, sex, region of the country, season, income and degree of urbanization, and was present in each age-sex-race subgroup. Gasoline lead level was a significant predictor ($p < 0.001$) of blood lead level after controlling for age, race, sex, degree of urbanization, income, season and region of the country, both in all groups and separately for blacks, whites, white males, white females, white children, white teenagers and white adults.

In a paper presented at the International Conference on Heavy Metals in the Environment (Schwartz, 1983) and in a recent EPA paper (Schwartz et al., 1984), we presented the results of a study of the relationship between blood lead and gasoline lead levels. We employed several data sets for this analysis, including a reanalysis of Billick's data and data from the NHANES II and the CDC lead poisoning screening programme. The statistical results indicated a highly significant regression coefficient for gasoline lead levels, which was consistent across all the data sets. Estimates of environmental lead from sources other than gasoline indicated that paint and other dietary lead sources were not the primary sources of the observed decline in average United States blood lead levels during the 1970's.

Gasoline lead was strongly associated both with the level of lead in human blood and with the prevalence of elevated blood lead levels. The association appeared to be causal because other factors, such as changes in dietary lead and paint lead, did not account for the changes in blood lead levels that have been associated with gasoline lead; the results suggested that more than one-half of the lead in the average American's blood in the second half of the 1970's was due to gasoline. Because gasoline lead usage in that period was restricted by regulation to about 60% of what otherwise would have occurred, those regulations appeared to have reduced substantially the average blood lead level in the United States and the number of children with lead toxicity.

Available Data Sets

Because gasoline sales and the use of various gasoline additives are regulated by federal law, information on them is available from the US Department of Energy and the EPA. Several data sets contain information on individual blood lead measurements. Most of these data sets target children in high risk groups who have been screened for lead poisoning. One data set, however, NHANES II, is a large representative sample of both adults and children in the United States. This section describes the data sets used to estimate the relationship between gasoline lead levels and blood lead levels.

Gasoline Use Data

We combined monthly data on national leaded gasoline sales (from the US Department of Energy) with quarterly average lead concentrations in grams per gallon (reported to EPA by refiners) to compute national monthly gasoline lead usage. For the Chicago, New York and Louisville areas we used gasoline sales data from the Ethyl Corporation's monthly survey of area gasoline sales, combined with national grams per gallon of lead, to obtain metropolitan gasoline lead usage.

The NHANES II

The data base for the regressions used to estimate the coefficients in our prediction models was the health and demographic information collected in the NHANES II survey. The US Bureau of the Census selected the NHANES II sample according to rigorous specifications from the US National Center for Health Statistics so that the probability of selection for each person in the sample could be determined. The survey used subjects chosen through a random multi-stage sampling scheme, designed to utilize the variance minimization features of a stratified random sample. A total of 27,801 persons from 64 sampling areas was chosen as representative of the United States non-institutionalized civilian population, aged 6 months through 74 years. Of those 27,801 persons, 16,563 were asked to provide blood samples, including all children 6 months through 6 years of age, and half of those aged 7 through 74 years. The non-respondent rate for blood samples was 39% and did not correlate with race, sex, annual family income or degree of urbanization.* A study of the potential non-response bias indicated that this was not a significant problem (Forthofer, 1983).

Lead concentrations in the blood of sampled persons and control groups were determined by atomic absorption spectrophotometry using a modified Delves Cup micro-method. Specimens were analysed in duplicate, with the average of the two measurements being used for the statistical analysis. Bench quality control samples were inserted and measured two to four times in each analytiecal run to calibrate the system. In addition, at least one blind quality control sample was incorporated with each 20 NHANES II blood samples. No temporal trend was evident in the blind quality control measurements (National Center for Health Statistics, 1981).

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* Because children were less likely to respond (51% of the children did not provide blood for lead determinations in the NHANES II data set), they were double-sampled. The weights used to adjust the data to the national population accounted for both the oversampling and underresponse of the children.

The NHANES II data did, however, display a marked relationship between blood lead and gasoline lead levels. Figure 2 plots gasoline lead and blood lead levels over time. Note how closely the changes in blood lead track the changes in gasoline lead, following both seasonal variations and the long-term downward trend. Figure 3 plots blood lead as a function of gasoline lead after controlling for age, race, sex, income, degree of urbanization, region of the country, educational level, smoking, alcohol consumption, occupational exposure, dietary factors and interactions among those factors; again, note the strong relationship.

Figure 2 NHANES II Data: Blood Lead versus Gasoline Lead (Feb. 1976 - Feb. 1980)

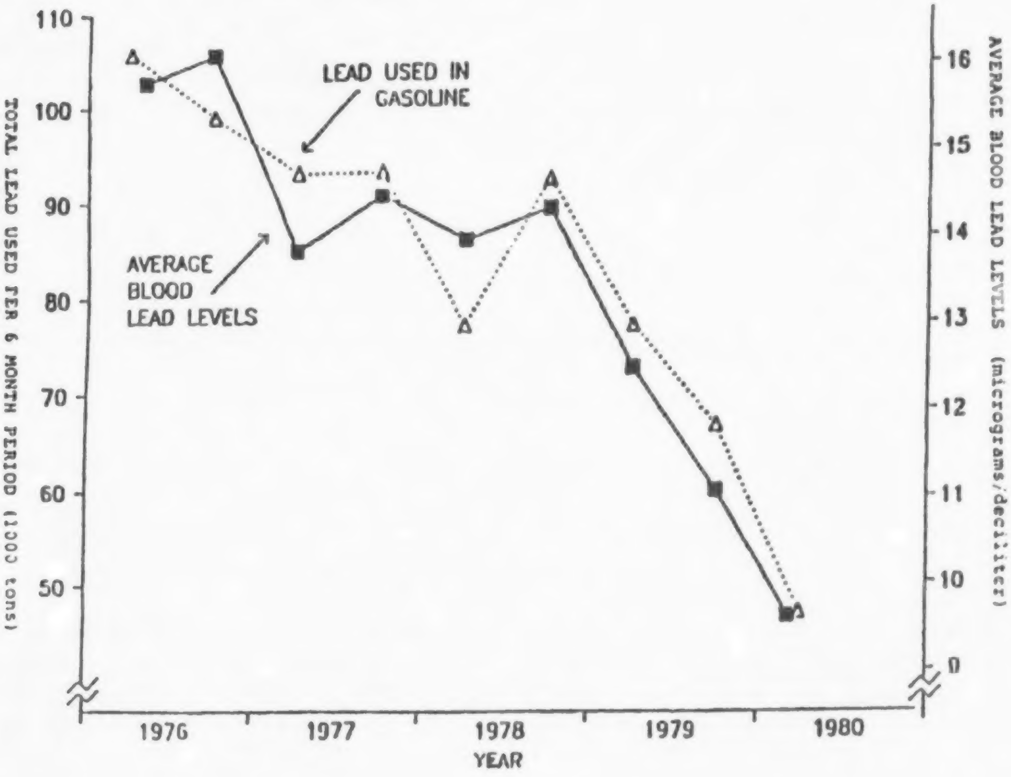
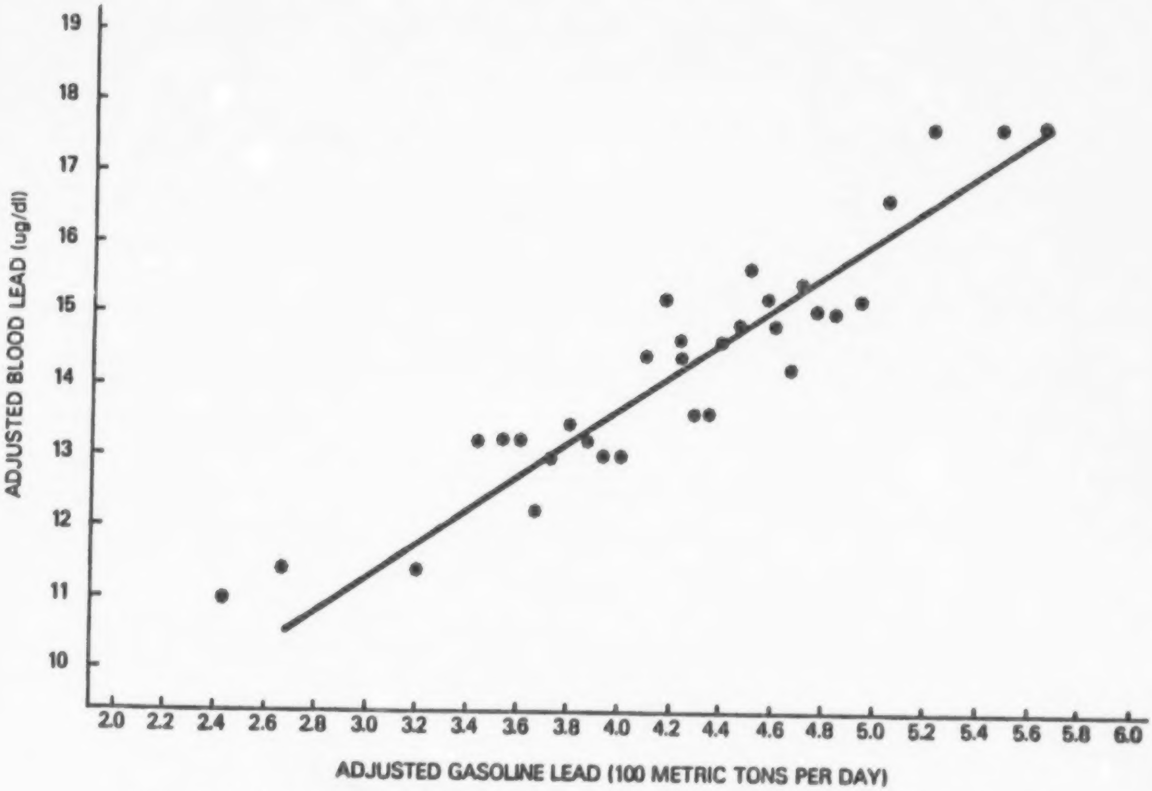


Figure 3 NHANES II Data: Blood Lead versus Gasoline Lead (adjusted)

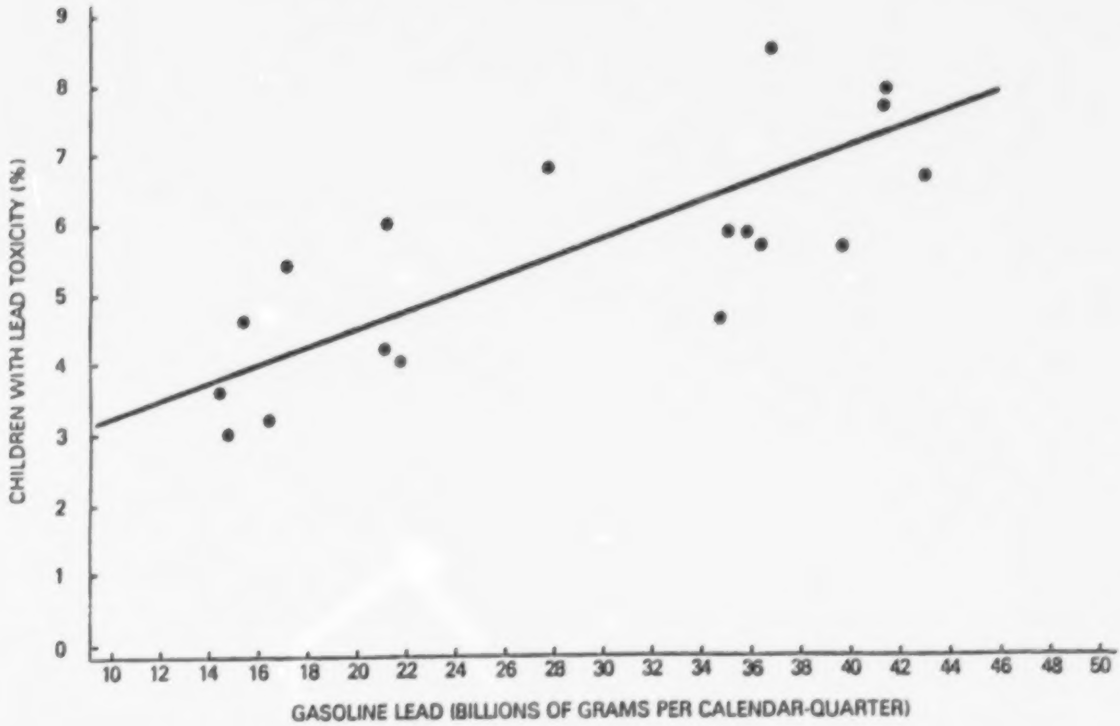


Note: Each point represents the average of approximately 310 observations. However the regression line shown is the true regression line for all 9987 individuals.

The CDC Screening Programme for Lead Poisoning

During the 1970's, CDC provided funds for community-wide screening programmes in many United States cities. Approximately 125,000 children were screened each quarter of the year. Results reported back to CDC included the number of children screened, the number with lead toxicity (defined as free erythrocyte protoporphyrin levels above 50 µg/dL and blood lead levels over 30 µg/dL) and the number with severe lead toxicity. Figure 4 shows a plot of gasoline lead versus the percentage of children with lead toxicity.

Figure 4 CDC Data: Gasoline Lead versus Percentage of Children with Lead Toxicity



Chicago, New York and Louisville, Kentucky Data

Billick (1982) analysed detailed data from the screening programmes in New York, Chicago and Louisville, including the average blood lead levels as well as the percentage of children with blood lead levels over 30 µg/dL. We have analysed these data further, focussing particularly on the Chicago data, which include a 1-in-30 sample of the over 200,000 blood lead screening tests performed in Chicago between 1976 and 1980. Figures 5 and 6 show the relationship between gasoline lead and blood lead levels in Chicago and New York, respectively.

Figure 5 Chicago Data: Gasoline Lead versus Blood Lead

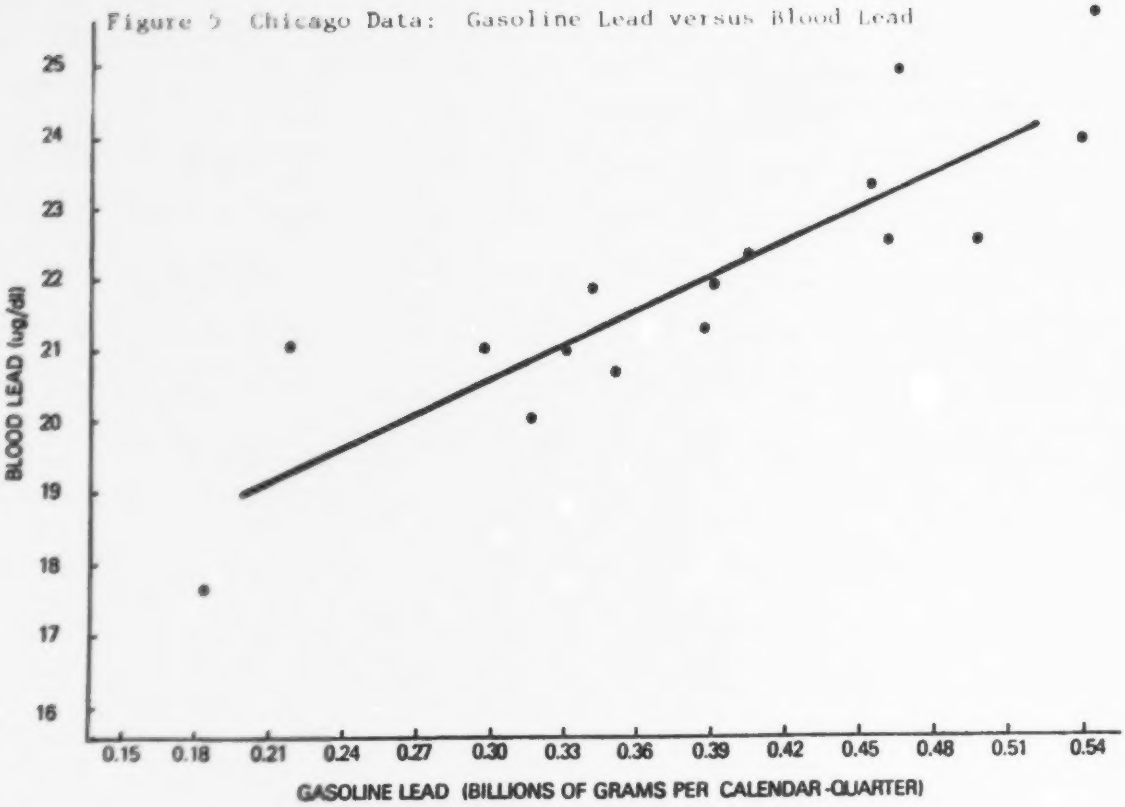
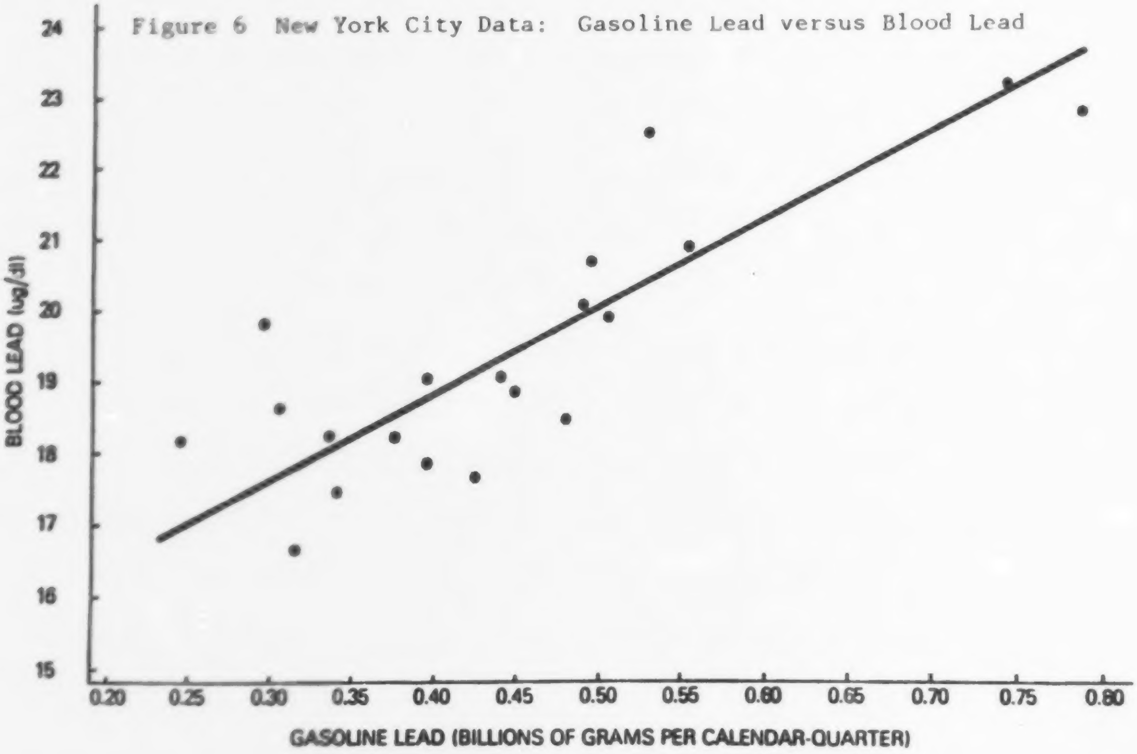


Figure 6 New York City Data: Gasoline Lead versus Blood Lead



Statistical Analyses of Exposure

We used multiple regression analysis to examine both the relationship between gasoline lead and individual blood lead levels and the relationship between gasoline lead and the probability of undue lead exposure (above 30 μg/dL) or lead toxicity (in the CDC data). For data from the NHANES II survey, we performed the analyses on individual blood lead measurements with the explanatory variables being gasoline lead, age, race, sex, degree of urbanization, alcohol consumption, smoking, occupational exposure, dietary factors, lead in canned food, region of the country, educational attainment, income, season of the year and interactions among these variables. We also ran separate regressions for various age, race and geographic groups. We weighted the results by the inverse of the probability of selection to produce nationally representative estimates. The regressions were run using a programme (SURREGR) designed to account for the stratified, clustered sampling procedure in the NHANES II survey, and many different specifications were considered.

Table 1 presents the results for the linear regression of gasoline lead and other explanatory variables on blood lead levels. (See Appendix 1 for definitions of the other variables.) Table 2 presents the results for the logistic regression on the probability of blood lead level over 30 μg/dL for children aged 6 months to 7 years. Table 1 shows that gasoline lead level was a highly statistically significant predictor of blood lead levels ($p < 0.001$, t-statistic > 60) even after accounting for potential confounding variables. The average value of gasoline lead usage was 426 t/day, suggesting that an average of about 9 μg/dL of blood lead was due to gasoline lead during that period. Additional regression results on the NHANES II data, including results for specific subgroups used in later analyses, are in Appendix 1.

Table 1.
NHANES II: regression results for whites.*

Effect	Coefficient	Standard Error	p-Value
Intercept	6.15		
Gasoline lead	2.14	0.037	0.0000
Low income	0.79	0.059	0.0025
Moderate income	0.32	0.034	0.0897
Child (under 8)	3.47	0.125	0.0000
Number of cigarettes	0.08	0.000	0.0000
Occupationally exposed	1.74	0.063	0.0000
Vitamin C	-0.04	0.000	0.0010
Teenager	-0.30	0.05	0.1841
Male	0.50	0.19	0.2538
Male teenager	1.67	0.26	0.0026
Male adult	3.40	0.26	0.0000
Small city	-0.91	0.085	0.0039
Rural	-1.29	0.10	0.0003
Phosphorus	-0.001	0.00	0.0009
Drinker	0.67	0.03	0.0007
Heavy drinker	1.53	0.10	0.0000
North-east	-1.09	0.11	0.0028
South	-1.44	0.14	0.0005
Mid-west	-1.35	0.25	0.0115
Educational level	-0.60	0.02	0.0000
Riboflavin	-0.188	0.005	0.0186
Vitamin A	0.018	0.000	0.0355

* The coefficients of the dummy variables show how much blood lead (in µg/dL) is, on average, attributable to a specific effect. The coefficient of gasoline lead shows how much blood lead (in µg/dL) is attributable to each 100 t/day of gasoline lead use.

Table 2.

Logistic regression* on probability of blood lead level greater than 30 µg/dL for children aged 6 months to 7 years.

Black Children: under 8 years old, 479 observations

Variable	Beta	Std. Error	Chi Square	P
Intercept	-6.9468	1.2656	30.13	0.0000
Gas lead	0.8633	0.2452	12.40	0.0004
Poor	0.9815	0.2803	12.26	0.0005
Age 1	1.1404	0.6246	3.33	0.0679
Age 2	1.1938	0.5696	4.39	0.0361
Age 3	0.5428	0.5728	0.90	0.3433

Dependent variable: 1 if blood lead is over 30 µg/dL; 0 otherwise
Model Chi square = 39.63 with 5 D.F.
Fraction of concordant pairs of predicted probabilities and responses = 0.718

White Children: under 8 years old, 2225 observations

Variable	Beta	Std. Error	Chi Square	P
Intercept	-8.1667	1.2322	43.93	0.0000
Gas lead	0.6331	0.2160	8.59	0.0034
Poor	1.2174	0.2935	17.21	0.0000
Age 1	1.4332	0.7978	3.23	0.0724
Age 2	1.7168	0.7415	5.36	0.0206
Age 3	1.1405	0.7503	2.31	0.1285

Dependent variable: 1 if blood lead is over 30 µg/dL; 0 otherwise
Model Chi square = 33.58 with 5 D.F.
Fraction of concordant pairs of predicted probabilities and responses = 0.637

* All logistic regression results were run using PROC LOGISTIC within the Statistical Analysis System (SAS). This procedure uses individual data where the dependent variable is 1 if the individual is above the threshold, and 0 otherwise.

For the CDC data, only quarterly data on the percentage of children screened with and without lead toxicity were available. We performed both weighted linear and logistic regressions on the probability of lead toxicity as a function of gasoline lead.

Tables 3a and b show the results of regressing the percentage of children with lead toxicity against gasoline lead for the 20 quarters between 1977 and 1981. 'Dummy' represents the period before CDC modified its definition of lead toxicity in 1978. The correlation coefficients between gasoline lead and the percentage of children with lead toxicity (0.8027) and between the change in gasoline lead and the change in the percentage with lead toxicity (0.817) were both very large, and the regression coefficient was highly significant ($p < 0.0001$). (The magnitude of the coefficient is not directly comparable with the NHANES II, because of both the difference in outcome variable--percentage toxicity versus blood lead level--and the difference in the units of gasoline lead.) The regressions predicted that if there had been no lead in gasoline at all, there would have been approximately 80% fewer cases of lead toxicity. This does not mean that 80% of the cases were due solely to gasoline lead, but rather that in 80 percent of the cases both gasoline lead and other exposures were required to bring children above the CDC definition of lead toxicity.

For the Chicago, New York and Louisville data, we performed logistic and linear regressions of the probability of blood lead levels being over 30 μg/dL for each race separately, with explanatory variables being age, season and gasoline lead level. Gasoline lead level was also significant, and explained the seasonal variation in elevated blood lead levels. We also regressed quarterly average blood lead levels in Chicago and New York against gasoline lead level, race, age and season. Table 4 shows the results of regressing the

Table 3a.

Regression of CDC screening data: percentage of children with lead toxicity on gasoline lead.

Variable	Coefficient	t-Statistic	Incremental r^2	p-Value
Constant	1.363	1.722	0	0.05
Gas lead*	0.1601	5.322	0.5215	< 0.001
Dummy	-1.036	-1.524	0.0427	0.07

$r^2 = 0.687$
Durbin Watson statistic = 1.786

Simple correlation coefficients:

	Gas Lead	Dummy
Percentage toxicity	0.8027	0.4068
Gas lead	-	0.6927

* Gasoline lead is in billions of grams per quarter. In the last quarter of 1978, gasoline lead use was 40 billion grams. By the second quarter of 1980, regulatory action had reduced this to 20 billion grams.

Table 3b.

Regression of CDC screening data: change in lead toxicity on change in gasoline lead.

Variable	Coefficient	t-Statistic	p-Value
Constant	0.3675	1.43	0.09
Delta gas lead	0.3938	5.84	<0.0001

$r^2 = .6670$
Durbin Watson statistic = 1.887

Simple correlation coefficient: 0.8167

Chicago data for black children for the 18 quarters from 1976 until mid-1980. (Our results differ from Billick's in that he had lead concentration values for only two quarters of the year and had to interpolate the others. We had lead concentrations for all four quarters, and, not surprisingly, using this better gasoline lead data gave a stronger relationship.) Again, gasoline lead level was an excellent predictor of children's blood lead levels ($p < 0.0001$). Auto-correlation corrections were run, and showed no significant correlation, nor did they produce a noticeable change in gasoline lead coefficients. Because the gasoline lead coefficient in Table 4 was in billions of grams per quarter for the Chicago area, we had to adjust from local to national units to compare it with the NHANES II results. Scaling by the ratio of Chicago's gasoline use to the nation's, and converting to the units used in the NHANES II regressions (100 t/day), the Chicago coefficient would correspond to a national coefficient of 2.08, which is essentially identical to the NHANES II results (a coefficient of 2.14, as shown in Table 1).

Regressions on all of the data sets showed that gasoline lead was an extremely significant explanatory variable both for individual blood lead levels and for the percentage of children with undue lead exposure or lead toxicity. Gasoline lead appeared to have accounted for 60% of the lead in Americans in the second half of the 1970's, and to have explained both the seasonal increases in blood lead levels from winter to summer and the long-term drop in blood lead levels during the late 1970's. EPA refinery reports show that the rate of decline in gasoline lead accelerated after late 1978, and this was paralleled by an accelerated decline in blood lead levels.

Table 4.

Black children in Chicago: regression of average blood lead levels on gasoline lead levels.

Variable	Coefficient	t-Statistic	Incremental r^2	p-Value
Constant	15.48	22.33	0	-
Gas lead*	17.02	11.27	0.5757	<0.0001
Age 1	0.85	1.53	0.0106	0.07
Age 2	1.68	3.03	0.0418	0.005
Age 3	1.01	1.84	0.0153	0.05
Age 4	0.66	1.20	0.0065	>0.10

$r^2 = 0.6194$
Durbin Watson statistic = 2.01

Simple correlation coefficients:

	Gas Lead	Age 1	Age 2	Age 3	Age 4
Average blood lead	0.7587	0.0009	0.01615	0.0337	0.0342
Gas lead	-	0	0	0	0

* Gas lead is lagged 1 month behind quarterly gasoline lead in billions of grams. The average for this period in Chicago was 0.379 billion grams.

Gasoline lead had the same coefficient in rural areas, in urban areas and in urban areas with populations over one million. In the NHANES II regressions, a dummy variable for residence in central cities versus suburban areas was not statistically significant. The gasoline lead variable that best correlated with blood lead was gasoline sales for the preceding month.

The Question of Causality

Although not crucial to a rule designed to be precautionary in nature, we did examine whether there is a causal relationship between gasoline lead and blood lead levels. In epidemiology there are several general criteria for determining whether association represents causality (Lilienfeld and Lilienfeld, 1980; Kleinbaum et al., 1982). The most useful criteria are:

- is there experimental evidence to support the findings?
- do several studies replicate the results?
- does a dose-response relationship exist?
- are there consistent effects in different types of studies?
- does cause precede effect?
- is the model biologically plausible?
- is it unlikely that other factors not included in the analysis would change the results?

We addressed these issues in turn, with particular emphasis on the last one, as no study can ever measure all possible confounding factors.

Experimental Evidence

Facchetti and Geiss (1982) investigated the contribution of gasoline lead to blood lead levels in Turin, Italy, during the late 1970's by changing the isotopic composition of the lead added to gasoline and monitoring the isotopic composition of blood lead. This isotopic lead experiment indicated that changes in the isotopic composition of air lead followed closely and rapidly changes in the isotopic composition of gasoline lead. Changes in the isotopic composition of blood lead also paralleled changes in gasoline lead. Based on modeling of the results, Facchetti and Geiss estimated that at least 25% of the (high) blood lead levels in Turin were due to gasoline lead; this was at least 6 μg/dL. Because blood lead isotopic ratios were still changing when the gasoline isotopes were switched back, the actual impact of gasoline lead is probably higher.

Manton (1977) analysed isotopic changes in blood lead in the United States and found the contribution of airborne lead (predominantly gasoline) was between 5 and 10 μg/dL in most of his subjects.

Tera et al. (1985) recently analyzed the isotopic ratios of blood lead in children in Washington, D.C., as the isotopic ratio of air lead changed. Their data showed that as late as 1983 at least 38% of the lead in children's blood still came from gasoline lead, despite the 50% reduction in gasoline lead since 1978.

Our analysis of the impact of gasoline lead indicated that in the late 1970's about 9 μg/dL of blood lead resulted from the lead in gasoline. This magnitude of effect is similar to that found in the isotope studies.

Does Cause Precede Effect?

One way to determine whether the trend in blood lead was caused by gasoline lead or was due to another variable is to examine the lag structure in light of our biomedical knowledge. The half-life of lead in the blood is about 30 days (Rabinowitz et al., 1976). Because the average blood test occurred on the 15th day of the month, the current month's gasoline lead would have had only 15 days to affect blood lead levels, and so, although significant, should have a lesser impact. The previous month's gasoline lead, on the other hand, represents emissions on average 15-45 days prior to examination, and as direct inhalation and even dust exposure show up rapidly in the blood, we would expect this 1-month-lagged gas lead to be more significant, with a noticeably higher coefficient. Similarly, we expected gasoline sold 2 months previously to be less significant and of lesser magnitude. If gasoline sales were merely a proxy for time, however, all 3 months should be equally good predictors, as t, t-1 and t-2 (where t is the month since commencing the survey) equally represent the passage of time.

We regressed the individual blood lead levels in the NHANES II survey against current, 1-month-lagged and 2-month-lagged gasoline lead simultaneously, and found 1-month-lagged gasoline lead was most significant and 2-month-lagged gasoline lead was least significant. This suggested that the causal model was correct. The coefficient of 2-month-lagged gasoline lead was one-half that of 1-month-lagged gasoline lead, which matches the 1-month half-life of lead in the blood.

Replicability and Consistency

We replicated our analysis of the national NHANES II data with our analysis of the site-specific Chicago and New York screening data and with Billick's analysis of the screening data from Chicago, New York and Louisville. In addition, Rabinowitz and Needleman (1983) examined umbilical cord blood from over 11,000 consecutive births at Boston Women's Hospital between 1979 and 1981. They found a strong association ($p < 0.001$) with gasoline lead used in the Boston area, and also that 1-month-lagged gasoline lead had the highest correlation. No significant monthly variation was noted in the mothers' education levels, smoking or drinking, and water lead levels increased somewhat over the period, while blood lead and gasoline lead levels fell. Thus, both local and national data from different studies collected by different investigators show the same pattern of gasoline lead levels being significantly related to blood lead levels.

The results of studies of both individual blood lead levels and average blood lead levels were consistent with analyses of elevated blood lead levels.

Billick examined the probability of blood lead levels above 30 μg/dL in Chicago, New York and Louisville, and found a strong relationship with gasoline lead. We repeated that analysis using logistic regressions, with the same results. Our investigation of the national CDC screening programme data, using both linear and logistic regressions, found the probability of lead toxicity was strongly dependent on the amount of lead in gasoline. Finally, we performed logistic regressions on the NHANES II data of the probability of both black and white children (under 8 years) and pre-teenagers (ages 8-14) having over 30 μg/dL of blood lead, and again found a strong relationship with gasoline lead levels.

Does a Dose-response Relationship Exist?

To assure ourselves that the linear relationship we found was the true form of the dose-response relationship, we divided the NHANES sample in half. We repeated the regression for whites in the second half of the survey period, when the average gasoline lead levels were roughly 50% of those in the first half. The gasoline lead coefficient was essentially unchanged at 1.94 (compared with 2.14 for the full sample). This indicated a stable linear relationship.

For blacks, the sample size was too small to divide the sample, so we used an alternative procedure. We regressed log (blood lead) against demographic variables and log (gasoline lead), for a range of zero gasoline intercepts. This model chose the best exponent for the relationship blood lead = (gasoline lead)^B. For the intercept (8 μg/dL) with the highest r^2, the exponent was 0.98, indicating a linear dose-response relationship. A square-root regression was also tried, and gave an inferior fit to the linear regression. The Chicago data, as noted before, gave the same magnitude of gasoline lead's effect on blood lead and visual examination of the regression plots in Figures 3 to 6 confirms the linearity in the relationship.

Biological Plausibility

Gasoline lead produced 90% of the emissions of lead into United States air in the 1970's, and it was the major source of lead contamination of the environment. Lead is emitted as predominantly respirable particulates (less than 1 μm) from auto exhausts. Respirable particulates reach the lung and show a high absorption rate. Gasoline lead is a major source of lead in street and household dust and in soil contamination, and, therefore, in addition to direct inhalation, results in secondary exposure through the inhalation and absorption of dust. Roels et al. (1976) showed a high correlation between blood lead and lead on the hands, presumably from air and dust contamination. Lead is known to be absorbed from both the lung and gut. Thus, the relationship of gasoline lead to blood lead is biologically plausible.

Control for Confounding Factors

Billick's analysis of children controlled for age and race, and our reanalysis controlled for season as well. The Annest et al. (1983) analysis of the NHANES II data controlled for age, race, sex, income, degree of urbanization, region of the country and season.

We used several approaches to control for confounding factors. Where we had sufficient information, we included potential confounding factors, or surrogates for them, in our regressions. In addition, we examined external data to check for changes in confounding factors that might bias our results, and performed several internal statistical checks to examine the likelihood of misspecification error.

External Validation

A great deal is known about the sources of lead exposure in the United States. The major general sources of body lead are food, water and paint. Although we have limited data on the specific sources of exposure of the individuals in our data sets, if all other general exposures were, on average, constant during the period, the effects of these would be part of the constant term in our regressions. Bias would occur only if these sources changed over the period.

The US Food and Drug Administration's estimates of lead in the diet (based on market basket surveys) during the NHANES II period are shown in Table 5. As there was no downward trend in dietary lead intake, this was unlikely to have been a potential source of bias in the model. Lead in canned food did change during the period, and we included a variable for this in our regression model. Dietary variables were used to represent differences in food consumption between individuals, which were also accounted for by age, sex, race, income, education and regional variables.

Table 5.

Lead in the diet (μg/day).

Fiscal Year	Infants	Toddlers	Males aged 15-20
1976	21	30	71.1
1977	22	28	79.3
1978	25	35	95.1
1979	36	46	81.7
1980	--	--	82.9

The exposure to lead from water is predominantly a function of pH levels. The pH of United States drinking water supplies appeared to have been constant over the 4- to 5-year period of our data.

Change in lead paint exposure in the United States was also an unlikely source of bias for several reasons. Firstly, adult blood lead levels decreased by almost as much (37% versus 42%) as children's blood lead, and adults generally do not eat paint. Secondly, because ingestion of lead paint usually results in the absorption of enough lead to produce large increases in blood lead, we would expect a drop in paint lead exposure to reduce blood lead levels only in people whose levels are above the mean. However, the drop in blood lead recorded in the NHANES II data shifted the entire distribution dramatically. Indeed, even low blood lead groups showed major declines in blood lead. This would not have occurred if ingestion of paint lead were the determinant.

Thirdly, the drop occurred across United States geographical boundaries, in suburbs as well as central cities. (Suburbs have a lower fraction of pre-1950 housing stock, and, therefore, inherently less exposure to lead paint, yet they showed the same drop and the same gas lead coefficient.*) Finally, lead paint removal programmes during this period reached only 50,000 of the 30 million United States housing units with lead paint (less than 0.2%), so exposure was unlikely to have changed in this period (CDC, 1976-80).

To lay these issues to rest, however, we did an additional analysis of the Chicago data. For each year of the screening programme, the CDC reported the percentage of lead-toxic children with a lead paint hazard in their home or the home of a close relative. In 1978, however, the homes of all screened children in Chicago (regardless of their blood lead level) were checked for lead paint hazard. This survey of over 80,000 housing units established the general prevalence of lead paint exposure in the screened population. With the probability of lead paint in the house, given lead toxity, and the probability of lead paint in the house in general, we used Bayes Theorem to compute the probability of lead toxicity given lead paint in the house, and the probability of lead toxicity when lead paint was not in the house. We then regressed these quarterly probabilities on gasoline lead. The results are shown in Table 6.

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* Shier and Hall (1977) analysed over 2500 housing units in Pittsburgh and found that the fraction that had lead paint concentrations above 2 mg/cm^2 decreased from over 70% in pre-1940 housing to about 43% in 1940-59 housing, and to 13% in post-1960 housing.

Table 6.

Chicago probability of blood lead level greater than 30 µg/dL with and without lead paint hazard in the home.

	Variable	Coefficient	t-Statistic	p-Value
Without lead paint hazard	Constant	-2.087	-0.6583	0.26
	Gas lead	35.398	4.423	0.0005
With lead paint hazard:	Constant	12.80	0.579	0.30

As we expected, gasoline lead was a more significant explanatory variable for children not exposed to lead paint than for the exposed group. Over 80% of the children were not exposed to lead paint at home, and among them gasoline lead was highly significant and explained most of the elevated blood lead levels. It was also striking that even among children with an identifiable lead paint hazard in their homes, gasoline lead was still strongly related to the probability of lead toxicity.

Seasonality

United States blood lead levels were strongly seasonal, with summer levels substantially higher than winter levels. However, when the NHANES II data were tested with seasonal variables, none of them was statistically significant, or even close to significant, when gasoline was included--the highest F-statistic for any season was 0.82. This indicated that the same gasoline lead coefficient successfully explained both the short-term increases in blood lead levels from winter to summer and the long-term decrease in blood lead levels over the 4-year period. The six regressions on the Chicago, New York and Louisville data, as mentioned before, also indicated that seasonality was insignificant once gasoline lead was in the model. This suggested that other long-term trends in lead exposure cannot have biased the gasoline coefficient, as the short-term and long-term gasoline coefficients were the same.

Other Time Trends

To test the hypothesis that there was another unknown lead factor that was decreasing over the period, and whose effects might be attributed to gasoline in our regressions, we repeated our analysis with time as a variable; time was entered as the number of days after February 1, 1976, that a blood sample was taken.

The results indicated that time was not significant when gasoline lead was in the regression. Moreover, the effect of gasoline lead on blood lead was reduced by only 23% if we kept the insignificant time variable in. In addition, the Chicago data for average blood lead were analysed with time as a variable. Here, again, gasoline lead was significant ($p < 0.02$) whereas time was insignificant ($p > 0.30$). We also tested time-squared on the CDC data and found it was insignificant.

Geographic Sampling Pattern

To be certain that the pattern of geographic sampling over time in the NHANES II period did not produce changes in blood lead level that the regression falsely attributed to gasoline, we included dummy variables for four regions of the country in our analysis. To check further, we inserted dummy variables for all 48 locations identified by the US National Center for Health Statistics (NCHS). NCHS did not release locational data for 16 counties with populations below 100,000; these were all represented by one additional dummy variable. Rerunning the regressions with these identifiers changed the gasoline lead coefficient by only about 5%, which was insignificant.

This result was extraordinary, because the NHANES II sampled different cities at different times, and the regression allowed the differences in blood lead levels over time to be attributed to changes in city location rather than gasoline lead. This meant that the coefficient of gasoline lead was heavily determined by the month-to-month changes in blood lead and gasoline lead within each city during the 2 months spent at each site. Yet the results did not change.

In addition, we performed a regression that had an interaction term between gasoline lead and the city identifiers. This procedure allowed a different slope in the gasoline lead/blood lead relationship for each county. The regression still yielded a coefficient for national gasoline lead of 1.83 ($p < 0.0001$).

Finally, the fact that analyses of many individual cities across the country (Boston, Chicago, New York and Louisville) yielded similar results suggested geographic location was not an important source of bias.

Subgroup Analysis

To verify the robustness and stability of the relationship between gasoline lead and blood lead, we ran regressions of the NHANES II data for several demographic groups separately. This was done both to verify that we properly controlled for these variables and to investigate whether the observed drop in blood lead levels was, in fact, due to a universal exposure such as gasoline lead, or could have been due to a source primarily affecting certain subgroups. The stability of the gasoline lead coefficient across these subpopulations reduced the likelihood of a specification bias.

This was because the bias introduced into the gasoline coefficient due to an omitted variable would be proportional to the regression coefficient that variable would have had if included. If the gasoline lead coefficient was insignificantly different among the regressions run for different subgroups, the omitted variable either must not have significantly biased the gasoline lead coefficient or must have been coincidentally constant among all the demographic groups. The only known such variables were gasoline lead and food lead.

We performed separate regressions for males, females, adults and children, for cities with populations over one million and for smaller urban areas. The maximum pair-wise difference in the gasoline lead coefficient among the six subgroups was less than 10%. In addition, we changed the definitions of large city (from over 1,000,000 to over 250,000) and rural (to include rural areas of cities under 10,000), and of the age categories. The coefficient of gasoline lead changed by only 2% when we performed this regression. The stability of our findings, given the many additional tests we conducted, testifies to the robustness of the relationship between blood lead and gasoline lead. In addition, a study of Annest et al. (1983) of the US Public Health Service, also using data from the NHANES II, found that the only reasonable explanation for the decline in United States blood lead levels was the decline in the amount of lead in gasoline. The Centers for Disease Control, the epidemiological branch of the Public Health Service, has also endorsed this relationship in its comments on this proposed rule (US EPA, Public Docket EN 84-05) and EPA's 1982 lead phase-down rule-making.

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Appendix

Regression results: whites with solder used in food cans.

Effect	Coefficient	Standard Error	p-Value
Intercept	4.16	--	--
Gasoline lead	2.16	0.04	0.0000
Low income	0.78	0.06	0.0024
Moderate income	0.36	0.03	0.0383
Child	3.47	0.11	0.0000
Solder	0.74	1.01	0.4651
Teenager	-0.32	0.05	0.1667
Male	0.68	0.08	0.0251
Male teenager	1.38	0.13	0.0005
Adult male	3.89	0.11	0.0000
Small city	-0.82	0.11	0.0212
Rural	-1.32	0.12	0.0007
Drinker	0.83	0.03	0.0000
Heavy drinker	2.09	0.09	0.0000
North-east	-1.02	0.13	0.0091
South	-1.15	0.17	0.0084
Mid-west	0.88	0.29	0.1093
Education level	-0.93	0.02	0.0000

9. DIETARY LEAD INTAKES

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Introduction

Humans are exposed to lead from numerous sources, including food, water and air. Among these, dietary intake is considered to be the major contributor of lead to the total lead intake (Kirkpatrick and Munro, 1982). Of interest in this respect are the absolute amounts of lead ingested via the diet and the individual sources of lead within the diet. This information is used to determine the relative risks involved with lead intake and whether there are options available to reduce lead intakes.

This report briefly gives the results of the latest research in the Health Protection Branch of Health and Welfare Canada on the dietary intake of lead by Canadian adults and infants.

Analytical Methodology

The quality of dietary intake studies relies heavily on the accuracy and detection limits of the methodology used to determine the levels of elements in foods. Dust and reagent contamination problems, coupled with naturally low levels and numerous interferences, have made low-level lead determinations particularly difficult (Patterson and Settle, 1976). An example is the variation in the results obtained for a single sample of milk powder distributed by the International Atomic Energy Agency. Results from 12 different laboratories ranged from 17 ng/g (nanograms lead in one gram of food, or parts per billion) to 246,500 ng/g, over 4 orders of magnitude (Dybczynski et al., 1980) (Table 1). Inaccurate analyses and/or poor detection limits can seriously affect the accuracy of total diet studies, particularly for a bulk-consumed food such as milk.

Table 1.

Analytical results reported by different laboratories for a single sample of milk powder.*

Lab.	Level (ng/g)	Lab.	Level (ng/g)
1	3000	7	170
2	17	8	150
3	583	9	438
4	2355	10	44
5	246500	11	77
6	660	12	29700

* Data used with the permission of the International Atomic Energy Agency, Vienna.

A great deal of time and effort has been spent by the Health Protection Branch to improve lead determination (Dabeka, 1982), and these efforts are continuing. Recently, a new method based on graphite furnace atomic absorption spectrometry has enabled us to analyse lead at levels as low as 0.05-0.1 ng/g in some foods (Dabeka and McKenzie, 1985). This method has been used by our laboratory to assist in certifying the lead level in milk powder standard reference material (SRM 1549), prepared by the US National Bureau of Standards. Our reported value of 19.7 ng/g agreed well with that of 19 ng/g found by isotope dilution mass spectrometry.

Quality control of analyses was assured by recovery studies and correction for recovery, inclusion of standard reference materials certified for lead level and of multiple blanks, and interlaboratory accuracy comparisons.

Intake of Lead by Adults

Dietary intakes of lead by adults were estimated using a duplicate diet study (Dabeka et al., 1985). Pre-cleaned sampling bottles, to encompass 10 food categories, were sent to each of 24 Canadian adults residing in Halifax, Montreal, Toronto, Winnipeg and Vancouver. Individuals were requested to order or prepare twice as much food as they usually ate, and to add to the sample bottles, classified by food type, exact duplicates of whatever they ate or drank during a 24-h period. None of the participants was to be on a diet, and no care was to be taken to ensure nutritional balance. At least one of the meals was to be prepared in the home. The foods were then weighed and analysed for lead to obtain both the individual intake from each food category and the total intake for each individual.

The resulting lead intakes, which include drinking water, ranged from 22 to 150 µg/day for individuals (Table 2), and averaged 54 µg/day or 0.80 µg/kg/day (Table 3). These levels were well below the FAO/WHO provisional tolerable daily intake (PTDI) of 7.1 µg/kg. Differences among cities were not statistically significant. The mean lead intake of 54 µg/day found in this study was about one-half of those of 106 µg/day (Méranger and Smith, 1972) and 138 µg/day (Kirkpatrick and Coffin, 1974) estimated earlier by the Health Protection Branch in Canada. The possible reasons for these differences are (i) differences in the way the dietary intake studies were designed, (ii) the use of (100-500 times) more sensitive analytical methodology for lead in this study, and (iii) improvements in canning procedures since the previous studies were done (Kirkpatrick, 1985).

Table 2.

Dietary lead intakes by Canadian adults.

	Intake			Intake	
City	µg/day	µg/kg/day	City	µg/day	µg/kg/day
Halifax			Montreal		
1 M[*]	22	0.33	11 M	62	1.05
2 M	150	1.84	12 F	54	0.96
3 F[*]	42	0.57	13 F	26	0.45
4 F	60	0.85	14 M	42	0.56
			15 M	90	1.02
Toronto			16 F	23	0.39
5 F	24	0.44			
6 M	38	0.48	Vancouver		
7 M	38	0.57	17 F	44	0.69
8 F	25	0.44	18 F	25	0.49
			19 M	43	0.56
Winnipeg			20 F	70	1.30
9 M	46	0.67	23 M	26	0.44
10 M	73	1.08	24 M	103	1.28
11 F	103	1.26			
12 F	63	1.39			

[*] M signifies male participant, F female.

Table 3.

Summary of lead intakes by adults.

City	µg/day	µg/kg/day
Halifax	69	0.90
Montreal	50	0.74
Toronto	31	0.48
Winnipeg	71	1.10
Vancouver	52	0.79
Mean (all participants)	54	0.80
Median (all participants)	43	0.57

Lead levels among food categories and even among foods within a single category varied widely (Table 4). The major sources of lead in the diet were cereals (15.3), beverages (15.4%), non-starchy vegetables (16.9%) and meat and fish (16.6%) (Table 4).

Table 4.

Lead levels (ng/g) in food categories and contribution (%) of category to overall dietary lead intake by adults.

Category		Mean*	Median*	Range*	% of Total**
I.	Cereals	33.7	32.4	12-78	15.3
II.	Water consumed directly	8.8	2.0	0.25-71	4.1
III.	Coffee, tea, beer, soft drinks	10.9	8.8	0.05-29	15.4
IV.	Fruit juices, fruits	17.9	7.9	1.5-109	9.6
V.	Dairy products, ice cream, eggs	8.9	3.3	1.2-82	4.5
VI.	Starch vegetables, rice, potat.	21.8	16.9	5.5-84	6.4
VII.	Other vegetables, tomato prod.	49.3	31.7	0.62-254	16.9
VIII.	Meat, fish, poultry	42.6	31.3	11-121	16.6
IX.	Misc. pie, chocolates, candy	117.6	33.1	14-1381	7.6
X.	Cheese (other than cottage)	653.9	33.8	28-6775	3.5

* Values taken over all category samples with foods in them.
** Contributions to diet calculated using all samples, including sample bottles left empty by participants.

Although the mean and median levels of lead in drinking water and its contributions to the total dietary intake of lead were generally small, drinking water contributed a significant amount of lead to the intake by three

Table 5.

Contribution of drinking water to dietary lead intakes by adults.

Parameter		Lead Level (ng/g)	% Contribution
Mean		8.8	4.1
Median		2.0	1.4
Individuals:	5	71.2	26.0
	16	16.2	15.7
	18	27.4	19.7

individuals from different cities (Table 5). These percentage contributions did not include water used in preparing foods in the home.

Finally, the intake data enabled us to partially evaluate the effect of the presence or absence of lead-soldered canned foods on lead levels in two food categories (Table 6). For both the fruit and non-starchy vegetable categories, lead levels were higher if the samples contained at least one canned item. The statistical significance of the effect was 99% for the fruits and 96% for vegetables.

Table 6.

Effect of lead-soldered cans on lead levels (ng/g) in two food categories.

	No items canned			One or more items canned			Level of significance
Category	n	mean	median	n	mean	median	
Fruits and juices	14	6.4	6.2	7	34	23	99%
Non-starch vegetables	12	26	19	7	88	70	96%

Dietary Intake of Lead by Infants 0-1 Year Old

Dietary intakes of lead by infants were calculated by analysing nine food categories for lead, and by using Nutrition Canada (1977) food intake data to calculate intakes. The levels of lead found in the individual categories (Table 7) ranged from 1.12 ng/g for cow's milk to 90 ng/g for cereals. The weak points in the above data were the lead levels in powdered infant formulae, for which the value (17 ng/g) of only a single sample of milk powder was used, and in cereals. Cereal results were obtained in a previous study (Kirkpatrick et al., 1980) using a method with a detection limit of roughly 20-50 ng/g. Also, the food intake data (Nutrition Canada) were gathered in 1972. Since that time, feeding patterns have changed, and several infant food

Table 7.

Infant food categories and lead levels used for estimating dietary lead intakes by infants.

Category	No. of Samples	Mean (ng/g)
1. Concentrated liquid infant formula	43	21
2. Meat and meat dinners	29	20
3. Vegetables and vegetable combinations	24	9
4. Fruits and desserts	24	16
5. Juices and drinks for infants	24	10
6. Infant cereals	35	90
7. Evaporated milk	8	72
8. Cow's milk (retail)	68	1.12
Human milk	200	1.04
Ready-to-use formula, glass bottled	20	2.58
Ready-to-use formula, canned	17	44
9. Formula, powder concentrate	1	17
10. Table foods	202	26

products, such as ready-to-use formulae and powder concentrates of vegetables, fruits, etc., were not on the market and were not included in the food intake study; other infant foods were often packed in lead-soldered cans. Finally, the levels of some elements can vary between items within a single food category as well as between manufacturers. Although the infant foods were collected at the point of manufacture with due consideration to sales volume, not all products were included, and there may be instances when the mean for a food category does not reflect the mean according to actual consumption patterns.

Mean levels of lead found in milks and infant formulae ranged from 1.04 to 72 ng/g (Tables 7 and 8). Cow's milk and human milk had the lowest lead levels, as did glass-bottled infant formulae which were fed in hospitals (Dabeka et al., 1986). Canned ready-to-use formulae, on average, had 17 times more lead than glass-bottled formulae, and lead levels were found to vary among manufacturers. For one manufacturer, 'C', lead levels in canned formulae were consistently low, and inquiries revealed that the cans were sealed without solder. For this manufacturer, the formula constituents appeared to be the main source of lead, because the mean level in concentrated liquid formulae was twice that in the ready-to-use formulae. For the other manufacturers, this ratio was not approximated, and the source of the lead appeared to be the solder used for sealing the cans.

Table 8.

Lead levels (ng/g) in infant formulae, cow's milk, and human milk.

Product	No.	Mean	Median	Range
Cow's milk (retail)	68	1.12	1.19	0.01-2.5
Human milk	210	1.04	0.55	0.01-15
Ready-to-use formula, glass-bottled	20	2.58	2.20	0.1-22
Ready-to-use formula, canned	17	44.2	30.1	1.5-149
- manufacturer A	3	42.0	26.0	21-79
- manufacturer B	11	56.4	36.2	3.7-122
- manufacturer C	3	1.7	1.6	1.5-2
Concentrated liquid formula	30	21.0	15.9	1.2-67
- manufacturer A	9	24.1	22.3	14-30
- manufacturer B	9	31.4	27.5	11-58
- manufacturer C	8	3.5	2.4	1.2-10

The mean lead levels for each food category were used to calculate dietary intakes of lead by infants (Table 9). The first row represents a composite lead intake by infants across Canada. Quite often an infant may be fed only one type of formula, and the following rows represent the effect of this on lead intakes. These were calculated by grouping all the milk and formula categories into a single category. Lead intakes varied by as much as a factor of 9.8, depending on the specific milk or formula given to the infant and the age group of the infant.

Table 9.

Effect of specific foods on dietary intake of lead by infants.

	Intakes (µg/kg/day by age, in months)					
Food Choice	0-1	1-3	4-6	7-9	10-12	0-12
All formulae, except RTU*	2.79	2.41	2.04	2.11	1.78	2.23
Conc. liquid infant formula	2.00	2.62	2.54	2.60	2.49	2.45
Canned ready-to-use formula	5.11	5.85	5.50	5.31	4.51	5.26
RTU formula, glass-bottled	0.68	1.26	1.28	1.45	1.64	1.26
Evaporated milk, canned	4.73	5.45	5.13	4.98	4.26	4.91
Cow's milk	0.53	1.10	1.13	1.31	1.53	1.12
Human milk	0.52	1.09	1.12	1.31	1.53	1.11

* Ready-to-use.

The composite intake for infants averaged over their first year was 2.23 µg/kg/day, about one-half that estimated previously for Canadian infants (Kirkpatrick et al., 1980; Kirkpatrick and Munro, 1982). The reason for this difference appeared to be the use of more sensitive analytical methodology in this study. Specifically, our average human and cow's milk levels were 20 times lower than the detection limit of 20 ng/g used in the previous studies. The differences this made on intake calculations can be inferred from Table 9.

The lead intakes of infants consuming glass-bottled infant formulae or cow's or human milk were low, averaging, respectively, 1.26, 1.12 and 1.11 µg/kg/day. These can be assumed to be intake levels for infants not exposed to lead from canned formulae. Infants consuming canned ready-to-use formulae had intakes averaging 5.3 µg/kg/day. For these infants, about 77% of their dietary lead intake can be attributed to lead-soldered cans in which the infant formulae were stored. On average, for infants 0-1 year old consuming only a specific type of infant formula, every 10 ng/g lead in ready-to-use formula increased the dietary lead intake by 0.96 µg/kg/day. Every 10 ng/g lead in concentrated liquid formula increased the lead intake by 0.48 µg/kg/day, excluding any contribution from water used for dilution of the formula.

The food intake data did not include drinking water as a separate item, and an evaluation of the total contribution of lead in the drinking water to the dietary intake of lead by infants could not be made. It was possible, however, to estimate the contribution to lead intake of drinking water used to dilute concentrated liquid infant formulae or evaporated milk. On average for infants 0-1 year old who consumed concentrated liquid formula or evaporated milk, every 10 ng/g lead in the drinking water contributed 0.48 µg/kg/day lead to the diet. For example, if the infant was fed evaporated milk containing 72 ng/g lead (Table 7) and the household water contained the average lead level of 8.8 ng/g (Table 5), the dietary lead intake of the infant in its first year of life would average 4.91 µg/kg/day, which is below the FAO/WHO PTDI of 7.1 µg/kg. If the water contained 71 ng/lead, however, the intake would be 7.91

µg/kg/day, which exceeds the FAO/WHO PTDI. Although 71 ng/g lead in the drinking water may appear high, it is still below the lead levels reported for three Canadian communities (Neri et al., 1977), and is equal to the level found in the water of one participant of the duplicate diet study for adults described above.

The above illustrates that there can be instances where some Canadian infants are exposed to dietary intakes of lead which exceed the FAO/WHO PTDI. This does not include intakes due to environmental sources, such as pica, automotive exhausts, soil and dust, which in some instances can be very high (Kirkpatrick and Munro, 1982).

Conclusions

If one assumes the FAO/WHO PTDI of 7.1 µg/kg/day as a benchmark against which to compare lead intakes, then the dietary intakes by Canadian adults are relatively low. The dietary intakes of lead by infants, however, are 2.8 times higher than for adults. Those infants fed canned ready-to-use formulae had a mean lead intake of 5.3 µg/kg/day (6.6 times the adult intake), approaching the PTDI of 7.1 µg/kg recommended by the FAO/WHO. The FAO/WHO figure, however, includes lead not only from food, but from all sources including air and water, and was estimated only for adults. Infants absorb from their food about 5 times more ingested lead than adults (Nutrition Foundation, 1982), and if this is interpreted with respect to lead intakes by infants and the FAO/WHO PTDI for adults, then the average infant in Canada consumed the absorption-adjusted equivalent of 11.15 µg/kg/day (5 times the mean intake over all age groups of 2.23 µg/kg/day), which exceeds the FAO/WHO PTDI of 7.1 µg/kg for adults. This may be a conservative estimate for many infants because it includes neither ready-to-use formulae nor the effects of feeding the infant only a canned formula.

As some of the more subtle toxicological effects of lead are only now being understood (Grant, p. 467; Rosen, p. 203), it is vital that steps be taken to reduce exposure of infants to lead from both food and environmental sources as quickly as possible. Regarding only food sources, lead-soldered cans in which formulae are stored appeared to be the major contributor to the intake of lead by infants.

Acknowledgements

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10. CHILDHOOD LEAD POISONING IN THE UNITED STATES -- A HISTORICAL PERSPECTIVE, AND THE CURRENT CONCERNS FOR THE METABOLIC EFFECTS OF 'LOW LEVEL' LEAD EXPOSURE

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Historical Background

Approximately 20 years ago the clinical picture of the child with acute lead intoxication was being recognized as a burgeoning problem in many of the large urban areas in the United States, primarily those in the north-eastern part of the country. In fact, many publications that focussed on this public health problem often referred to the area from Washington, D.C., to Boston as the 'leadbelt'. The typical scenario often included a young pre-school child, usually from a lower socio-economic status, often black, who may or may not have been known to exhibit pica. In the majority of instances, these children would be living in dilapidated old housing units, mostly pre-World War II, in which multiple layers of lead-based paint would have been commonly used. The use of lead-based paint would be common on both interior and exterior surfaces; in the dilapidated conditions that usually existed, the paint would be freely peeling and chipping from multiple surfaces. The concentration of lead in such painted surfaces would commonly range from 10 to 30% by dry weight (100,000-300,000 ppm).

As young pre-school children would often ingest paint particles of high lead concentration or mouth surfaces painted with lead-based paint, their blood lead levels would often become greatly elevated. Not infrequently, symptoms of lead intoxication would become manifest, beginning usually with gastrointestinal complaint and often progressing to neurological symptoms including those of frank encephalopathy. Many children with lead encephalopathy would arrive at a medical facility with frank seizures or even in a comatose state. A significant proportion of those children with lead encephalopathy would die, and those who survived would often exhibit permanent serious neurological sequelae. These sequelae could range from seizure disorders to severe mental retardation requiring institutional care.

Lead Poisoning Prevention

In the early 1970's, various methodologies were developed and perfected whereby large numbers of children in susceptible populations could be screened in order to detect blood lead elevations prior to the onset of symptoms. As it had been determined that a significant percentage of those children who developed symptomatic lead poisoning were left with serious sequelae, the reasoning that followed, therefore, was that early detection of blood lead elevations before the onset of symptoms could improve the overall outlook. In 1971 and 1972 the US Public Health Service undertook a 27-city survey in which young pre-school children in high-risk neighbourhoods in 27 cities throughout the United States were screened for blood lead elevations. Of all of the children between the ages of 1 and 5, 9.1% were shown to have blood lead levels that exceeded 40 μg/dL, and in this same survey over 95% of the homes that were screened were shown to contain lead-based paint on interior or exterior surfaces. In a similar study done in the State of Illinois in 1971, over 6000 young pre-school children were screened for blood lead elevations; overall, 19% of these children in 14 different Illinois cities had elevated blood lead levels. Other studies confirmed these findings, and it soon became apparent that children with potentially toxic levels of lead in their systems were not just limited to the large urban centres in the north-eastern United States.

In the early and mid-1970's, the US Public Health Service began funding programmes throughout a number of communities in the United States that were designed to systematically screen high-risk children and detect those children at greatest risk before the onset of symptoms. In addition, an important part of these screening projects was the screening of the children's dwelling units so that environmental correction could be undertaken and potentially harmful lead-based paint could be removed from these children's environments. During the rest of the 1970's, the Public Health Service through its childhood lead programme actively funded between 65 and 70 childhood lead poisoning prevention projects throughout the United States.

By the late 1970's, clinicians throughout the country were beginning to report a dramatic decrease in the incidence of children with symptomatic lead poisoning, especially those with encephalopathy. It soon became apparent that children with dramatically elevated blood lead levels (80 µg/dL or more) were becoming less common, and attention then shifted to those children whose blood lead levels were still elevated but were generally found to be entirely asymptomatic.

As more investigators became interested in those children with intermediate blood lead elevations, it became apparent that other routes of lead intake must be responsible for these elevations. Generally those children with frank pica had extremely elevated blood lead levels and were often symptomatic. A number of investigators, including Sayre and his colleagues (1974) and Hammond and his colleagues (p. 27), were able to demonstrate that there was a good correlation between the amount of lead that could be removed from children's hands and that in their bloodstreams. In other words, the hypothesis was made and was generally accepted that children who lived in an environment where there was excess lead available, usually thought to be derived from lead-based paints, chronically ingested lead that was on their hands in normal hand-to-mouth activity. Figure 1 shows composite data from two different studies, one in Cincinnati and one in Brussels, Belgium, indicating close correlations between hand lead of young children and their blood lead concentrations (Roels et al., 1980).

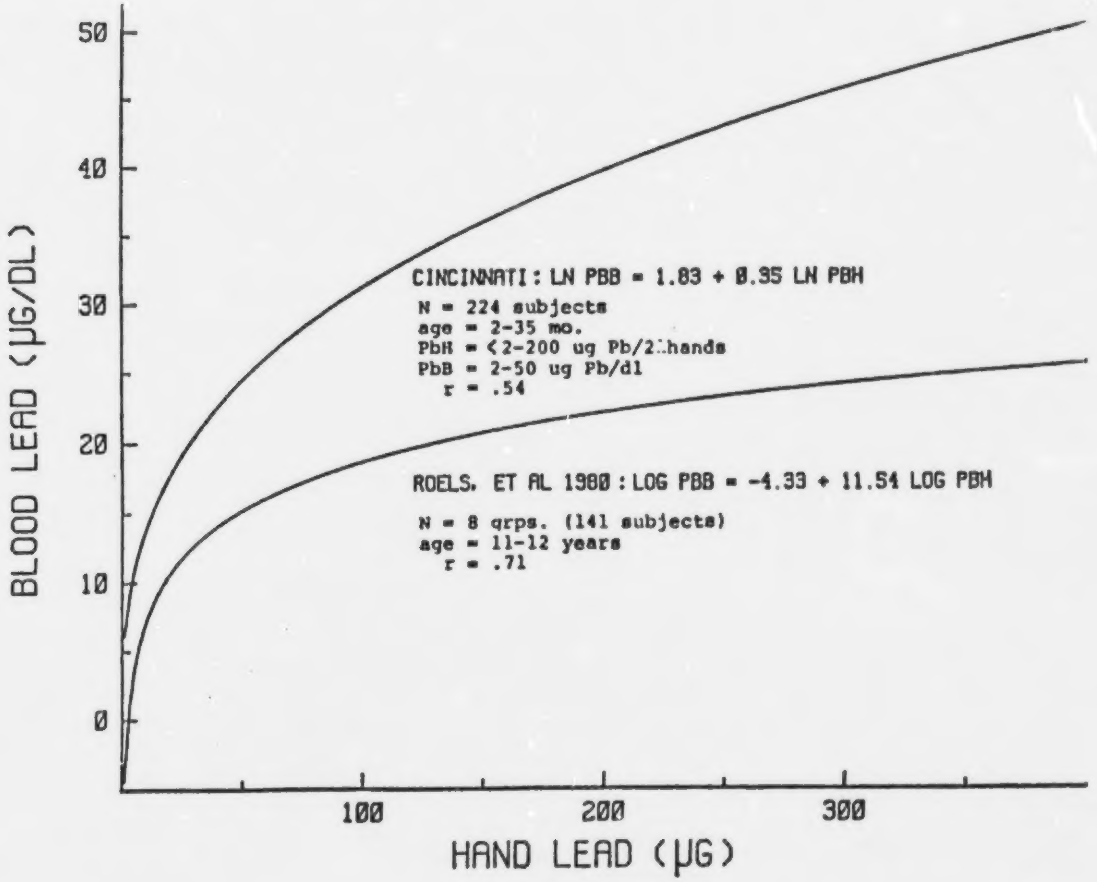

Figure 1. Relationship between Children's Hand Lead and Blood Lead

Blood Lead Levels and Housing

In recent years, Chisolm (1983) in Baltimore and Hammond and his group in Cincinnati (p. 27) have clearly shown that elevated blood lead levels in young urban children are very closely related to the type of housing in which they live. Both groups have demonstrated that children who live in post-World War II 'lead-free' housing usually have blood lead levels in the normal range. In contrast to this finding, those children who live in old and deteriorating housing are often at increased risk for developing elevated blood lead levels. In the symptomatic study, those children living in 'lead-free' public housing had blood lead levels that remained in the normal range, whereas those children living in pre-World War II housing demonstrated a pattern of increasing blood lead levels through 18 months of age (Figure 2). In a similar study in

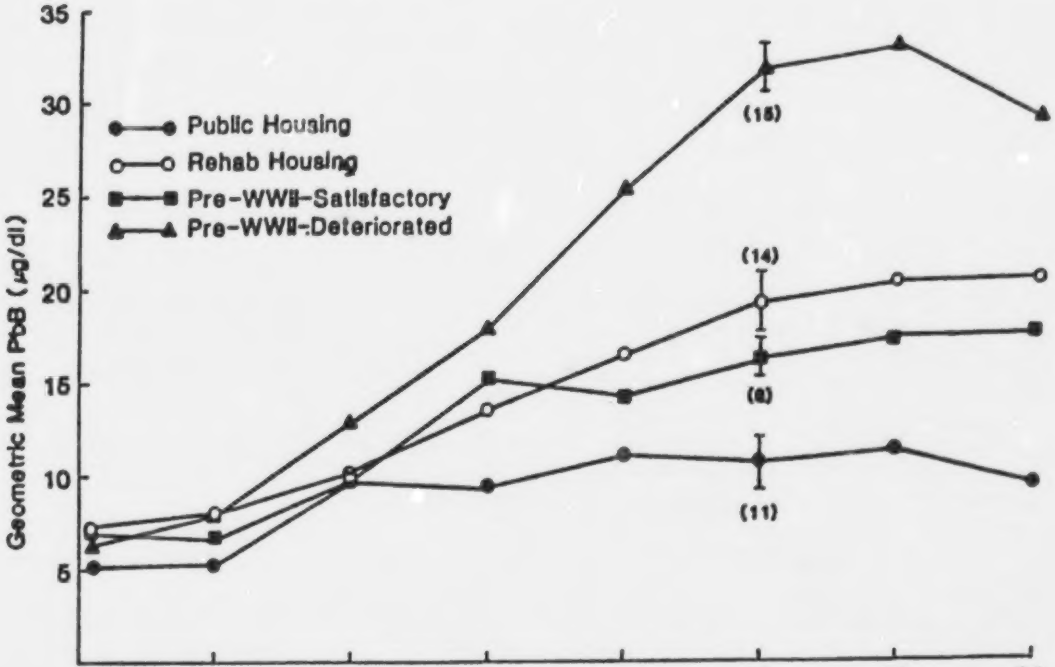

Figure 2. Blood Lead by Housing Type and Age

Baltimore, Chisolm (1983) followed a large number of children who were discharged from the hospital after an initial course of chelation therapy for elevated blood lead levels. Only 4 out of 112 children who were discharged to lead-free public housing developed recurrent blood lead elevations after 1 year, whereas all 57 children who returned to old, deteriorated housing containing lead-based paint developed recurrences by 9 months. All of these children, regardless of the type of housing in which they lived, were similarly exposed to other sources of lead, including petrol, so that the case for blood lead elevation being associated with lead-based paint is a convincing one.

Metabolic Effects and 'Low Level' Lead Exposure

Limited time does not permit a thorough discussion of the myriad of 'low level' lead effects that a number of people have commented about in recent years, but several examples will be briefly examined.

Vitamin D - Calcium - Lead Interactions

Several reports have been published over the past few years noting the reduction of the active form of vitamin D, 1,25-dihydroxyvitamin D, with increased blood lead levels in young children. In a 1980 report, Rosen et al. reported that this biologically active form of vitamin D was decreased in two groups of children with elevated blood lead levels: those who were asymptomatic had blood lead levels ranging from 33 to 55 µg/dL, and those in a group with significant lead overexposure had blood lead levels between 62 and 120 µg/dL. A control group of children with blood lead levels ranging between 10 and 26 µg/dL had normal values of 1,25-dihydroxyvitamin D. The reduction of 1,25-dihydroxyvitamin D in those children with significant blood lead elevations was in the order of that seen with children with renal rickets, whereas the reduction seen in those children with intermediate blood lead elevations was less significant. In addition, these intermediate children had serum calcium and parathyroid hormone levels similar to those children in the control group, indicating that there was no biological effect noted accompanying the intermediate depression of 1,25-dihydroxyvitamin D. The question arises as to whether these changes represent a normal biological response to the interaction of lead and vitamin D or, as some would contend, an adverse biochemical effect at low lead levels. Careful examination of the available studies reveals that this question has not been definitively answered. In fact, Rosen (1984) stated that the initial reduction of 1,25-dihydroxyvitamin D may actually serve as a protective mechanism, as it results in not only reduced intestinal absorption of ingested lead but also possible reduced lead deposition in soft tissues, including the kidney and brain.

Inhibition of Pyrimidine-5-Nucleotidase (Py-5-N)

It has been noted that the red blood cell enzyme Py-5-N shows reduced activity across a broad range of blood lead levels, with inhibition being observed at blood lead levels as low as 10 µg/dL. Some have contended that this represents an adverse health effect at a very low blood lead level. Valentine, who has elucidated much of the original information involving the interaction of lead and this enzyme, recently commented to the US EPA about this contention, and suggested unequivocally that there is no evidence whatever that the depression of Py-5-N activity at blood lead levels below 30-40 µg/dL constitutes an adverse health effect. To quote Valentine in his submission to the US EPA:

> Certainly there is no body of evidence indicating that reducing Py-5-N per se has deleterious effects at blood lead levels below 30 to 40 µg/dL or indeed at levels substantially higher than this.... The 'threshold of

harm' bears little relationship to the 'threshold of statistical detectability'.

As laboratory methodologies have been perfected in recent years, a considerable number of enzyme interactions with lead have been more completely understood. The above interactions involving lead and the vitamin D endocrine system as well as the red blood cell enzyme Py-5-N are merely two of these enzyme systems where lead has been shown to have an interaction. As those methodologies are perfected, changes in these enzyme systems are being detected across a wide range blood lead levels, but, as previously indicated, these changes *per se* do not necessarily represent any clear-cut evidence of adverse health effect. Further work needs to be done to elucidate the meaning of these findings and to differentiate simple biological changes from those representing adverse health effects.

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11. AN OVERVIEW OF

METABOLIC AND CELLULAR EFFECTS OF LEAD: A GUIDE TO 'LOW-LEVEL' LEAD TOXICITY IN CHILDREN

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Introduction

Environmental lead exposure, with its concomitant risk of toxicity, remains a major health hazard for children in the United States. Even 'low' levels of lead are associated with a wide range of metabolic disorders and with neuropsychological deficits (Needleman et al., 1979; Rosen et al., 1980; Mahaffey et al., 1982a; Angle et al., 1982; Piomelli et al., 1982; CDC, 1985a; EPA, 1985; Rosen, 1985). Despite efforts at eliminating lead-based paints and the introduction of lead-free gasoline, an estimated 2.3 to 3.9 million American children between 9 months to 5 years of age have elevated blood lead concentrations (>25 μg/dL), according to the new guidelines from the Centers of Disease Control (Mahaffey et al., 1982a; CDC, 1985a; Yip and Dallman, submitted 1986). Based upon these CDC guidelines, about 9% of children in this age range have elevated blood lead concentrations (>25 μg/dL) that require medical intervention. The magnitude of this national health issue in children (rich, poor, white, black, city or country-based) was realized when the results of the Second National Health and Nutrition Examination Surveys (NHANES II) were published in 1982 (Mahaffey et al., 1982b). This representative cluster sample defined the incidence of elevated blood lead levels nationally in children of this age, and these data confirmed earlier impressions that blacks and disadvantaged, inner city children were affected disproportionately.

As a result of national screening programs, symptomatic high level lead toxicity has largely disappeared in American children. Such toxic effects include impairment in heme, vitamin D and red blood cell nucleotide metabolism. In addition, such effects have been demonstrated in children at blood lead values less than 25 µg/dL. This new disease of lead toxicity is now defined by the discrete abnormalities noted above. In addition, experimental studies have shown that lead perturbs calcium homeostasis in hepatocytes, bone cells and brain cells. As a result, the normal calcium messenger system may be placed beyond the stimulus-response cascades of multiple cellular processes (Rosen, 1983; Pounds, 1984; Pounds and Rosen, 1986). This new disease of lead toxicity in largely asymptomatic children has been redefined with sensitive techniques available to clinician-scientists in the 1980's. We define this disease today by highly sensitive and objective biochemical abnormalities--rarely by overt symptoms (Rosen and Chesney, 1983).

In this selective review, I will discuss some of the biochemical abnormalities that now define the disease of lead toxicity in American children. In so doing, as Chairman of the US Centers for Disease Control (CDC) Advisory Committee on Lead Poisoning Prevention, I will summarize most of the relevant data that recently led the CDC to lower the definition of an elevated blood lead level to 25 µg/dL. Lastly, I will review some of the data that are related to the unique susceptibility of children to the toxic effects of lead.

My framework is based upon formal pediatric training, and I consider it to be my responsibility to ensure the health and full growth potential of children. This is my special interest. As part of this task, to date I have formally treated about 1500 lead-toxic children with chelating agents over the past decade. We have an increasingly busy Lead Clinic at our Center, where 20 or more children are seen weekly. Between 125 and 140 children are admitted annually by my Division to the in-patient service for chelation therapy. Within this context, we have several ongoing, NIH-supported, clinical and basic research projects relating to the metabolism of lead in children and in monolayer cultures of osteoclasts and osteoblasts derived from mouse calvaria.

Prevalence

A nation-wide survey, conducted from 1976 to 1980, showed that children from all geographic areas and socio-economic groups are at risk of lead toxicity (Mahaffey et al., 1982b). Data from that survey indicate that 3.9% of all United States children under the age of 5 years had blood lead levels of 30 µg/dL or more. Extrapolating this to the entire population of children in the United States indicates that an estimated 780,000 children 6 months to 6 years of age have blood lead levels of 30 µg/dL or more. There was, in addition, a marked racial difference in those data. Two per cent of white children had elevated blood lead levels, but 12.2% of black children had elevated levels. Further, among inner-city black children and in families with annual incomes of less than $6000, the prevalence of blood lead levels of 30 µg/dL or more was 18.6%. Among white children in lower-income families, the prevalence of elevated lead levels was eight times that of families with higher incomes.

In 1984, EPA concluded that "there is a national health problem associated with exposure to environmental lead for the general population and, in particular, pre-school children" (EPA, 1984). Based upon data from the NHANES

II survey (Mahaffey et al., 1982b), the number of affected children (1-6 years of age) increases now to 2.3-3.9 million (Yip and Dallman, 1985), because CDC has lowered its definition of an elevated blood lead level to 25 µg/dL (CDC, 1985a). In view of the magnitude of this national health problem, CDC now recommends that all children (9 months to 6 years of age) be screened at least once annually (CDC, 1985a, b). As more children are screened for iron deficiency by erythrocyte protoporphyrin (EP) testing, simultaneous screening (for lead toxicity and iron deficiency) becomes feasible.

Sources

Previous estimates of the quantitative relationship between ambient air lead levels and blood lead levels need to be revised. Data reviewed extensively by Schwartz (p. 151) and Grant (p. 467) suggest that lead from leaded gasoline is a much more important contaminant than was previously thought. Data from NHANES II also indicate that leaded gasoline is a more significant source of 'background' lead that previously thought. Annest et al. (1983) correlated major reductions in the amounts of lead added to gasoline sold in the United States with significant reductions in children's blood lead levels. They found that between 1976 and 1980, the overall mean blood lead level in the United States population dropped from 14.6 to 9.2 µg/dL. A similar relationship between leaded gasoline sales and umbilical cord blood lead levels has been shown by Rabinowitz and Needleman (1982).

CDC (1985a) recently concluded that, "in terms of reducing background blood lead levels, removing lead from gasoline as rapidly as is feasible is probably the most important public health measure". Now that EPA is moving rapidly in this direction, our efforts in the United States must be directed to provide safe housing for children and to eradicate a high-level source of lead (lead paint) in 25 million household units (CDC, 1985a).

The Disease of Lead Toxicity in Asymptomatic American Children

Although children with increases in body lead stores are usually asymptomatic, it is likely that they have pervasive metabolic abnormalities involving heme synthesis (Piomelli et al., 1982), vitamin D (Rosen et al., 1980; Mahaffey et al., 1982a) and cortisol (Saenger et al., 1984) metabolism, red cell nucleotide metabolism (Angle et al., 1982) and subclinical neurobehavioural effects (Needleman et al., 1979; Yule et al., 1981; Winneke et al., 1983). Some of these profound metabolic and cellular effects of lead occur at blood lead concentrations less than 25 µg/dL (Rosen et al., 1980; Angle et al., 1982; Piomelli et al., 1982; Mahaffey et al., 1982a). Some of these adverse health effects of lead will now be discussed briefly.

Red Cell Porphyrins

Because lead is a generalized poison of SH groups and thereby interferes with several basic intracellular functions, lead damage is manifest by interferences with essential enzyme systems as well (Piomelli et al., 1982). The damage produced by lead on heme synthesis is of critical importance as a result of heme's participation in multiple basic processes. Measurements of erythrocyte protoporphyrin, the cornerstone for screening lead toxic children in the United States (Piomelli et al., 1982), reflects lead's impairment of the insertion of iron into the protoporphyrin molecule. This critical biochemical step takes place in mitochondria and is catalyzed by ferrochelatase. Because of lead toxicity in red cells, protoporphyrin gradually substitutes itself for heme in the hemoglobin molecule. In view of the fact that protoporphyrin fluoresces, measurement of erythrocyte protoporphyrin has become a simple, convenient and reasonably sensitive method for identifying lead toxic children with or without iron deficiency. Recent studies in children have demonstrated the accumulation of erythrocyte protoporphyrin at blood lead concentrations between 14-17 μg/dL (Piomelli et al., 1982).

6β-Hydroxycortisol

6β-hydroxycortisol (6β-OHF) is a highly polar metabolite of cortisol formed in the endoplasmic reticulum of hepatocytes. This metabolite is the major unconjugated urinary product of cortisol and constitutes 1-2% of total daily cortisol secretion. Inhibition of heme synthesis in the liver results in impairment of cytochrome P450 activity, an important component of the mixed function oxidase system. We have examined whether urinary excretion of 6β-OHF, formed by cytochrome P450-dependent oxygenase systems, may be abnormal in 26 children with mild to moderate increases in blood lead levels (23 to 60 μg/dL) (Saenger et al., 1984). We observed a highly significant negative correlations ($p < 0.001$) between 6β-OHF excretion and blood lead, EP and urinary lead concentrations $CaNa_2EDTA$ testing in a mixed group of children, some of whom had positive and others negative $CaNa_2EDTA$ tests, which is the current reference method for assessing lead stores in children and adults (Saenger et al., 1982; Markowitz and Rosen, 1984; Piomelli et al., 1984; Rosen, 1985). Analysis of 20 children with positive $CaNa_2EDTA$ challenge tests demonstrated that 6β-OHF was significantly depressed in lead toxic children compared to age-matched controls. Moreover, children who had negative provocative tests revealed similar 6β-OHF values to normal children. We link the results of this study to those reported by Piomelli and associates (Piomelli et al., 1982). A major fraction of the heme synthesized in the liver serves as the prosthetic group for the family of microsomal hemoproteins--the cytochromes P-450. These hemoproteins are the terminal oxidases of the liver mono-oxygenase system that metabolizes drugs and various foreign chemicals. We conclude that lead impaired the activity and/or diminished the content of cytochrome P450-dependent mono-oxygenases as a consequence of altered heme metabolism (Saenger et al., 1984).

Lead and the Vitamin D Endocrine System

1,25-Dihydroxyvitamin D Levels. We reported (Rosen et al., 1980) that lead-toxic children with blood lead concentrations between 33 and 120 µg/dL have marked reduction in serum values of the vitamin D hormone, 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$). The most striking decrease in circulating 1,25-$(OH)_2D$ levels was found in children whose blood lead levels were greater than 62 µg/dL. Nonetheless, highly significant depressions in circulating 1,25-$(OH)_2D$ levels were also found in children whose blood lead concentrations ranged from 33 to 55 µg/dL (Rosen et al., 1980). These findings were associated (in children whose blood lead levels were above 62 µg/dL) with a significant decrease in serum total calcium and ionized calcium, whereas serum parathyroid hormone (PTH) concentrations were significantly elevated. Under these two latter conditions, and in the face of decreased dietary intake of calcium, it is anticipated that the recognized modulators of 1,25-$(OH)_2D$ synthesis (PTH, Ca^{2+}, P_i) would enhance production of the vitamin D hormone. The opposite was found, suggesting impaired production of the vitamin D hormone, reflected by reduction in circulating concentrations.

Significant negative correlations between blood levels of both lead and EP and serum levels of 1,25-$(OH)_2D$ in children with blood lead concentrations between 33-62 and 62-120 µg/dL further support the view that the lead ion impairs the production of 1,25-$(OH)_2D_3$, as aluminum does in children undergoing total parenteral nutrition (TPN) (Rosen and Chesney, 1983).

In lead-poisoned children, 1,25-$(OH)_2D$ levels returned to normal shortly after chelation therapy, whereas serum 25-hydroxyvitamin D (25-OHD) levels did not change with treatment. In a follow-up study 2 years later, no difference was observed in the slope of the regression line for blood lead concentrations below or above 30 μg/dL (Mahaffey et al., 1982a); this negative correlation was observed (between blood lead and serum 1,25-$(OH)_2D$) over a range of blood lead values from 12 to 120 μg/dL.

At blood lead levels between 33 and 55 μg/dL (Rosen et al., 1980), serum 1,25-$(OH)_2D$ concentrations are reduced to an extent comparable with those observed in children who have completely lost two-thirds of their normal renal function. At blood lead levels ranging from 33 to 120 μg/dL, similar depressions in serum 1,25-$(OH)_2D$ (≥ 20 pg/mL) are found in: (i) vitamin D - dependent rickets, Type I--this is an inborn error of vitamin D metabolism in which the 1-hydroxylase enzyme system (or a component thereof) is virtually absent, (ii) oxalosis--an inborn error of metabolism that involves abnormal calcium/phosphate metabolism with severe renal damage, (iii) hormone-deficient hypoparathyroidism--this is an auto-immune disorder with absence of functioning parathyroid glands and impaired biosynthesis of 1,25-$(OH)_2D_3$, and (iv) aluminum intoxication in children on total parenteral nutrition--aluminum-contaminated solutions produce marked reduction in circulating 1,25-$(OH)_2D$. (These disorders are reviewed in Rosen and Chesney, 1983.)

The 1-hydroxylation step to produce the vitamin D hormone is carried out in the mitochondria of the renal tubule by a complex cytochrome P450 enzyme system (Rosen and Chesney, 1983). The ingredients of this enzyme system include intact mitochondria, Krebs cycle substrates, electron transport via the cytochromes P450, oxidative phosphorylation and generation of NADPH. The biosynthesis of the vitamin D hormone is controlled, in large part, by the functional integrity of mitochondria, by the ionic (Ca, P_i) micro-environment of the extra- and intracellular fluid and by the uptake of calcium by mitocondria (including the delicate homeostasis characteristic of intracellular calcium concentrations and calcium pumps). It is clear, therefore, based upon lead's toxic effects on mitochondria, cellular energetics and cytochrome P450 electron transport in several studies, including children (Piomelli et al., 1982; Saenger et al., 1984), that lead most likely impairs the 1-hydroxylase enzyme system; experimental studies directly support this view.

Depression in plasma 1,25-$(OH)_2D$ values was first reported by Smith et al. (1981) in rats fed lead acetate. Moreover, lead ingestion totally blocked the intestinal calcium transport response to the vitamin D hormone. A recent report extends these data further. Edelstein et al. (1984) reported that tissue levels of the vitamin D hormone are depressed in leaded chicks, and that kidneys (removed from such animals and subsequently studied in vitro) failed to convert 1,25-$(OH)_2D$ to 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$), compared with controls. These findings provide considerable support for the view that lead impairs the complex 1-hydroxylase enzyme via perturbations in ionic transport in cells and/or the functional integrity of mitochondria that carry out this 1-hydroxylation. In terms of ionic transport, current information indicates that increasing extracellular and intracellular concentrations of calcium depress production of the vitamin D hormone (Rosen and Chesney, 1983). If renal tubule cells accumulate high concentrations of calcium after exposure to lead, as do hepatocytes (Pounds et al., 1982a, b), osteoclasts (Rosen, 1983, 1985; Rosen and Pounds, 1985) and brain slices (Silbergeld and Adler, 1978; Silbergeld et al., 1980), renal tubule cells may consequently 'turn off' 1,25-$(OH)_2D$ production. Such an effect is likely to be reversible when lead is decreased in the extracellular fluid--as it is post-therapy in $CaNa_2EDTA$-treated children. In summary, lead's effect(s) on the complex 1-hydroxylase enzyme system may be expressed at one or several components of the enzyme (cellular energetics, heme-cytochrome metabolism, integrity of mitochondria, etc.). At the same time, lead may interfere with the ionic regulation of 1,25-$(OH)_2D_3$ biosynthesis.

Calmodulin and Calcium Homeostasis. The marked increase in knowledge of the vitamin D endocrine system has led recently to the recognition that the vitamin D hormone exerts its actions on cells and target tissues in a manner beyond its classical role of mineral homeostasis (bone, kidney, gastrointestinal tract). Some of these newly described actions of 1,25-$(OH)_2D_3$ will be summarized very briefly.

The vitamin D endocrine system is responsible, in large part, for the maintenance of extra- and intracellular calcium homeostasis (Rosen and Chesney, 1983). As a result, the integrity of cells of diverse function is preserved as well as numerous calcium-mediated functions. It is known that calcium, an important participant in the stimulus response cascades of many target cell systems, acts not only as a second messenger, but also as a modulator of cyclic nucleotide metabolism. The temporal and spatial regulation of cellular calcium is exceedingly important in the response of a variety of cells to hormonal and electrical stimuli.

The discovery of calmodulin led eventually to the recognition of its centrality as an intracellular calcium receptor protein. Its discovery and its nearly universal distribution in mammalian cells emphasized further that calcium serves as a 'universal' second messenger. As such, calmodulin regulates several enzyme systems and transport processes (Cheung, 1982). The list of calcium-sensitive reactions modulated by the calmodulin-calcium complex is rapidly expanding (Cheung, 1982). Recently, it has been shown that lead can replace calcium in the activation of calmodulin-sensitive processes (Cox and Harrison, 1983; Habermann et al., 1983). Although at an early stage of investigation, it is conceivable that a molecular model of lead toxicity may include (in addition to those cited above) occupation of calcium-binding sites on calmodulin. As calmodulin regulates multiple cell activities, such a mechanism may underlie some of the diverse effects of lead. Lead alone, and lead's interaction(s) with calmodulin and intracellular system homeostasis, are inherently coupled to the vitamin D endocrine system.

Tumour Cell Differentiation. Tumour cell lines possess cytosol receptors to which 1,25-$(OH)_2D_3$ binds specifically (Honma et al., 1983; Shiina et al., 1983). Human promyelocytic leukemia cells (HL-60) can be induced to differentiate *in vitro* by 1,25-$(OH)_2D_3$. The differentiation-associated properties, such as phagocytosis and C3 rosette formation, were induced by as little as 0.12 nM 1,25-$(OH)_2D_3$. As cells exhibited differentiation, the viable cell number was decreased to less than half of the control. A specific cytosol protein that bound 1,25-$(OH)_2D_3$ was found in these HL-60 cells, and its physical and biochemical properties closely resembled those found in 'classical' vitamin D target tissues.

1,25-$(OH)_2D_3$'s action to cause differentiation in HL-60 cells (and other cell lines) is a manifestation of the normal action of this steroid hormone to elicit maturation of myeloid stem cells into macrophages. Because macrophages are thought to be the precursor of bone-resorbing osteoclasts, this is a logical mechanism whereby 1,25-$(OH)_2D_3$ brings about calcium resorption/homeostasis through recruitment of cells competent in bone remodelling.

T and B Lymphocytes. 1,25-$(OH)_2D_3$ receptors are present in normal human monocytes and malignant lymphocytes, but are absent from resting T and B lymphocytes (Provvedini et al., 1983; Amento et al., 1984; Tsoukas et al., 1984). T and B lymphocytes obtained from normal humans express the 1,25-$(OH)_2D_3$ receptor when such cells are activated by mitogenic lectins and Epstein-Barr virus (Provvedini et al., 1983; Amento et al., 1984; Tsoukas and Manolagas, 1984). The mitogenic lectin phytohemagglutinin (PHA) stimulates T lymphocyte proliferation and induces the production of various lymphokines, including interleukin-2 (IL-2), which is important for the growth of T cells. Recently, it has been demonstrated that 1,25-$(OH)_2D_3$ (at picomolar concentrations) inhibited the growth-promoting lymphokine IL-2 and proliferation of PHA-stimulated lymphocytes obtained from normal humans (Tsoukas et al., 1984). These results confirm and extend earlier evidence that 1,25-$(OH)_2D_3$ receptors are expressed in T lymphocytes activated with mitogenic lectins. These new findings couple the endocrine and immune systems together, as exemplified by the suppressive effect of corticosteroids on immune function (Tsoukas et al., 1984).

The reduction in serum 1,25-$(OH)_2D$, also found in kidney disease and inborn errors of metabolism, in a wide range of lead-toxic children should be viewed within the context that the vitamin D hormone has several physiological actions at the cellular level. These include cellular calcium homeostasis in virtually all mammalian cells and associated calcium-mediated processes. In addition, the vitamin D hormone has newly recognized functions that involve cell differentiation and essential immunoregulatory capacity. It is reasonable to conclude, therefore, that impaired production (and deficiency) of the vitamin D hormone has profound and pervasive effects on multiple tissues and cells of diverse type and function.

Assessment of Lead Stores in Children by $CaNa_2EDTA$ Testing

Practical and effective tests for the diagnosis of lead poisoning have been developed. These include measurements of blood lead and EP (Markowitz and Rosen, 1984; Piomelli et al., 1984; Saenger et al., 1984; CDC, 1985a, b). Although the usefulness of blood lead and EP measurements for the diagnosis of lead toxicity is accepted, it is unclear whether these measurements are also sensitive indicators of the body burden of lead in the large number of individual children with mild to moderate increases in body lead stores (blood lead levels of 25-55 µg/dL) (Markowitz and Rosen, 1984; Piomelli et al., 1984; Saenger et al., 1984; CDC, 1985a, b); relatively few such children have been assessed to ascertain if they qualify for the same 5-day course of chelation therapy with $CaNa_2EDTA$ as those with lead poisoning (blood lead level greater than 55 µg/dL).

In studies carried out at this and other Centers, we have found that in milder forms of increased lead burden (CDC Classes II and IIIa), blood lead and EP levels failed to show a significant correlation with urinary lead excretion after $CaNa_2EDTA$ challenge (Markowitz and Rosen, 1984; Piomelli et al., 1984; Saenger et al., 1984). Similarly, other studies have observed this non-linear relationship between chelatable lead, blood lead and EP levels. Overall, depending on the series, about 30-40% of children in CDC Class II (mean blood lead level of 37 µg/dL) and 80-85% in Class III (mean blood lead level of 47 µg/dL) qualify for and are subsequently treated as if frank blood poisoning was initially present (Markowitz and Rosen, 1984; Piomelli et al., 1984; Saenger et al., 1984).

These data cast doubt on the usefulness of conventional screening tests as sensitive and early manifestations of elevated lead stores in individual children. They also demonstrate further that assessment of body lead stores by $CaNa_2EDTA$ testing--not achieved by blood EP or lead measurements--is of great importance in a large population (2.3-3.9 million) of American children with elevated blood lead levels. Stated differently, we and others (Markowitz and Rosen, 1984; Piomelli et al., 1984; Saenger et al., 1984; CDC, 1985a, b) have shown that the majority of individual children with elevated body lead stores (blood lead levels range from 25 to 55 µg/dL), despite only mild to moderate elevations in blood lead levels, have similar increases in the magnitude of body lead burdens as those observed in children with high-level lead toxicity (blood lead level greater than 55 µg/dL). Careful assessment of elevated body lead stores is essential to recognize those who require the same $CaNa_2EDTA$ treatment regimen as children with high-level lead toxicity (blood lead level greater than 55 µg/dL).

The biological half-time for lead in blood is relatively short and will reflect recent exposure. In cases where lead exposure can be reliably assumed to have been at a given level, such as in occupationally exposed adults, a blood lead measurement is more useful than in instances where some intermittent high-level exposure may have occurred, as in children. Evidence has accumulated in experimental and clinical studies that blood lead levels have significant limitations in reflecting both the amount of lead in target tissues (including the brain) and the temporal changes in tissue lead that occur with changes in exposure (Rosen, 1985). Stated differently, the observed nonlinearity between blood lead and chelatable lead is probably explained by the presence of a sizeable pool of bone lead labile to $CaNa_2EDTA$--but not reflected by blood lead concentrations (Rabinowitz et al., 19771 1980; Rosen and Markowitz, 1980; Rosen, 1983, 1985; Rosen and Pounds, 1985).

Based upon these considerations, CDC has placed increased reliance on the results of $CaNa_2EDTA$ testing in its new guidelines (CDC, 1985a, b) to determine which children who have blood lead levels between 25 and 55 µg/dL, require the same treatment as children whose blood lead levels are greater than 55 µg/dL.

In general, the new CDC guidelines (an elevated blood lead level greater than or equal to 25 µg/dL; elevated EP level greater than or equal to 35 µg/dL) were based upon:

- neurobehavioural deficits found in lead-burdened children (Needleman et al., 1979)
- toxic biochemical effects of lead on essential metabolic pathways involving heme, vitamin D and red blood cell nucleotide metabolism--at blood lead levels below 30 µg/dL, CDC's 1978 definition of an elevated blood lead concentration
- the results of $CaNa_2EDTA$ testing in asymptomatic children with blood lead levels between 30 and 55 µg/dL, which indicated that a significant fraction of such children qualified for the same treatment regimen as children with blood lead levels greater than 55 µg/dL; thus, CDC lowered its definitions of an elevated blood lead level to provide a wider margin of safety for hundreds of thousands of American children.

To this researcher, the new blood lead cut-off at 25 µg/dL is a relatively 'conservative' definition in view of the new evidence cited in making its decision at this level. This new definition does mean that EP testing can remain intact as the initial screening method for lead toxicity. EP screening is fast, simple, economical and can be carried out on capillary blood specimens. If the definition of an elevated blood lead level went below 25 µg/dL, then blood lead measurements from venous samples would have to replace EP screening, which is an insensitive measure of blood lead levels less than 25 µg/dL. The use of blood lead assays was considered to be unacceptable from a public health standpoint (cost, instrumentation, acceptance of venipunctures by parents, likelihood of a decrease in numbers of children screened).

Unique Susceptibility of Children to the Toxic Effects of Lead: Metabolic Considerations

Besides the presence of physiological states that result in a new homeostatic balance of lead and mineral metabolism (rapid skeletal growth and turnover in children, pregnancy), age *per se* is another important factor. Challenge of young rats with lead chelators produces lower total lead excretion in the urine than that observed in adult animals (Jugo, 1980). Although the overall mechanisms of differences in lead retention between young and older animals is unclear, these experimental studies support the view that lead metabolism in infants and young children places the young in far higher risk categories than older humans. Momcilovic and Kostial (1974) compared the distribution of ^{203}Pb in suckling and adult rats. Over an interval of a week, about 85% of the labelled nuclide was retained by the suckling rat compared with 34% in the adult; it is important to point out that the rate of long-term retention in mice is governed by the rate of lead release from bone (Keller and Doherty, 1980).

Comparative lead excretion and retention data are presented in Table 1. These data in children, compared with those in adults, reveal (i) that

Table 1.

Daily excretion and retention of lead in children and adults.

	Children*	Adults**
Dietary intake (µg/kg)	10.76	3.63
Dietary lead absorbed (%)	46	15
Dietary lead absorbed (µg/kg)	4.95	0.54
Air lead absorbed (µg/kg)	0.20 (estimate)	0.21
Total absorbed lead (µg/kg)	5.15	0.75
Daily urinary lead (µg/kg)	1.00	0.47
Absorbed lead excreted in urine (%)	16.00	62.00
Endogenous faecal lead (µg/kg)	0.50 (estimate)	0.24
Total excreted lead (µg/kg)	1.50	0.71
Percentage of intake retained	34.00	1.00

* Ziegler et al., 1978.
** Rabinowitz et al., 1977.

considerably more dietary lead is absorbed, which leads to a marked increase in overall lead absorption, (ii) the percentage of urinary lead/absorbed lead is low, and (iii) the retention of lead is considerably higher.

Based upon the data in Table 1, a 10-kg child will retain about 40 µg of lead daily. In reported studies (Barry, 1975, 1981), total lead accumulated in the skeleton between 2 and 14 years of age is between 8 and 18 mg, or a daily retention of 2-5 µg (or 6-14% of total retention). These reports and calculations may not, in fact, account sufficiently well for differences in the growth of the skeleton and lead retention in younger (less than 2 years) compared with older (greater than 2 years) children. In this regard, so-called 'normal' blood lead levels in children either parallel those in adult males or are 35% higher (in parallel) than those in adult females (Chamberlain et al., 1978). Moreover, Barry (1981) found that soft tissue lead content is similar in children who range in age from 1 to 9 years. Taken together, these studies in children suggest that (i) the concentration of lead in soft tissues, in relative terms, is not particularly 'elevated', (ii) a large labile bone lead pool exists that is kinetically distinct from the soft tissue compartment, (iii) the non-linear relationship between chelatable lead/blood lead and dietary lead/blood lead supports the view that blood lead concentrations *per se* are a relatively poor index of soft and hard tissue burdens in children (Rabinowitz et al., 1977, 1980; Chamberlain et al., 1978; Marcus, 1979, 1982; Rosen, 1983, 1985; Piomelli et al., 1984; Rosen and Pounds, 1985)--elevated lead intake can add substantially to the body burden and the chelatable pool without its recognition in blood lead measurements, and (iv) it is likely that dilution of the large quantity of skeletal lead by its tissue mass in children masks, to an extent, the contribution of skeletal lead to both blood and soft tissue compartments.

Summary

Pervasive toxic effects of lead have been demonstrated in children at blood lead concentrations only recently considered to be 'normal'. Such effects on heme and vitamin D metabolism have been reported at blood lead levels below 25 μg/dL. These abnormalities now define the disease of lead toxicity in hundreds of thousands of American children; companion studies have shown profound toxic effects of lead at the cellular level. These toxic effects of lead on normal metabolic pathways include perturbations of mitochondrial functioning and disturbances in the heme-cytochrome system of several cell types, including the P450 complement of enzymes and impairment in cellular transport of calcium. Metabolic pathways, enzymes and hormonal systems are perturbed by minute amounts of this remarkably toxic metal!

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12. THE HEALTH EFFECTS OF LOW-LEVEL EXPOSURE TO LEAD

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I am pleased to have this opportunity to contribute to the scientific data base on human lead toxicity and to its control. I believe the regulation of lead in the atmosphere may be among the most important public health decisions to confront the Canadian government. This issue has been the subject of intense and sometimes heated discourse in the United States. In 1977 and 1984, I was a consultant to the US EPA during the writing of the first and second EPA Air Quality Criteria for Lead documents. In reviewing the current literature in preparation for this review, I was struck by the extraordinary distance we have travelled in only 7 years in enriching the scientific data base on lead. We are in a much better position in 1985 to regulate lead than we ever have been.

In this brief review, I summarize the findings on the effects of lead at low dose on central nervous system (CNS) function in children, and then discuss some of the epistemic questions encountered in assessing whether or not lead is causally associated with neuropsychological deficit. I concentrate here on the work of my own group, but mention other studies in relation to the inferences we have drawn. There are a number of extensive reviews of this question (e.g. Needleman and Landrigan, 1981; Needleman and Bellinger, 1984).

Four studies conducted in the 1970's set the stage for the debate on the significance of the effects of low lead exposure. Landrigan et al. (1975), in a Centers for Disease Control study, measured IQ scores in a group of Mexican-American children living in the vicinity of a lead smelter, and found that those children with blood lead levels greater than 40 μg/dL had lower scores on the Wechsler Intelligence Scales for children compared with those subjects with blood lead levels below 40 μg/dL. In a lead industry-sponsored study of the same population, McNeil et al. (1975) evaluated two groups of children who were said to differ in their lead exposure. They found no differences between groups. Of the 206 children eligible for the study by McNeil et al., 67% were enrolled. Some of the non-participant families were litigating against the smelter at the time, raising the question of self-selection bias.

Perino and Ernhart (1974) compared black pre-schoolers with blood lead levels between 40 and 70 μg/dL with a control group with blood lead levels below 30 μg/dL on the McCarthy Scales of Infant Development. Covariates measured were birth weight, birth order, number of siblings, parental education and maternal IQ. This was the first study to examine maternal IQ as a covariate. This variate, with age and birth weight, was entered with lead into a multiple regression model. Lead was shown to be significantly associated with cognitive, verbal and perceptual scales of the test.

de la Burde and Choate (1975) followed children who had been enrolled in the forward collaborative perinatal study of the National Institutes of Health (NIH). Blood lead levels were obtained in children with a history of pica but not in age- and sex-matched controls. IQ scores were compared at 4 and 7 years of age. At 4 years of age, significantly more lead-exposed (LE) children were rated as defective and borderline than were controls. This was found to persist at the 7-year examination. At this time, LE subjects had twice the incidence of abnormal neurological examinations and had significantly more behavioural problems at home and at school. The strength of the study is the semi-prospective design. A weakness is the absence of blood lead levels in the control group, but this is to some degree compensated by the comparison of lead levels in dentine in both groups. This analysis confirms that the control group had significantly lower exposure.

Review of these studies and those not cited here shows that many shared to a greater or lesser extent the following problems in design or execution:

1) Use of an inadequate marker of lead exposure. Almost all studies relied on blood lead level to classify subjects, but because blood is a short-term storage system for lead, this could lead to misclassification of subjects and bias the study towards the null hypothesis.

2) Use of insensitive or inappropriate measures of outcome. In the search for effects at low dose, sensitive and appropriate measures of outcome are required.

3) Neglect of variates which could confound. Many factors influence the course of child development, and some of these may be correlated with lead exposure. Neglect of these factors could result in either a Type 1 or Type 2 error.

4) Neglect of the possibility of ascertainment bias. When less-than-complete sampling of the population is accomplished, it is possible that non-participant subjects may differ in some way related to outcome from those included in the study. This could result in spurious associations between independent variables or could result in missing a true association.

5) Lack of statistical power. A number of studies have sampled small groups and reported no significant effect. This may be due to lack of enough power to find a statistical difference even when the groups did differ.

In 1970 I set out to determine if children exposed to lead, but not recognized as such, were developmentally handicapped. It seemed clear that blood lead concentrations were markers of recent exposure, and could misclassify subjects if exposure had ended. We investigated the use of shed deciduous teeth as a marker of past exposure, and found that dentine lead levels were dramatically elevated in children who were lead-poisoned or who came from areas where lead poisoning was endemic. Suburban American children had lower levels than children from the inner city, but had higher levels than children from Iceland. Studies by investigators in Belgium and Norway have documented the validity of dentine lead as a classifier of exposure (Fosse and Justesen, 1978; Steenhout and Pourtois, 1981).

We collected shed deciduous teeth from 70% of children in two school systems in industrial towns near Boston (Steenhout and Pourtois, 1981). The populations in these towns were mostly white working-class families. The distribution of dentine lead levels from this sample of over 2000 children was log normal. We selected for neuropsychological follow-up children from the upper 90th percentile and the lowest 10th percentile for lead. Only subjects with concordant results on two separate analyses were included in the study. Excluded from participation were children who were born prior to term or who had a history of noteworthy head injury or lead exposure. Also excluded were families in which English was not the primary language. Included children were then invited to the neuropsychological laboratory at the Children's Hospital of Boston accompanied by their mothers and, while the child was studied, 39 covariates were scaled and evaluated. Of the 39 covariates, five (mother's age at subject's birth, mother's education, father's socio-economic status, mother's IQ and family size) differed at p less than 0.1 between high-

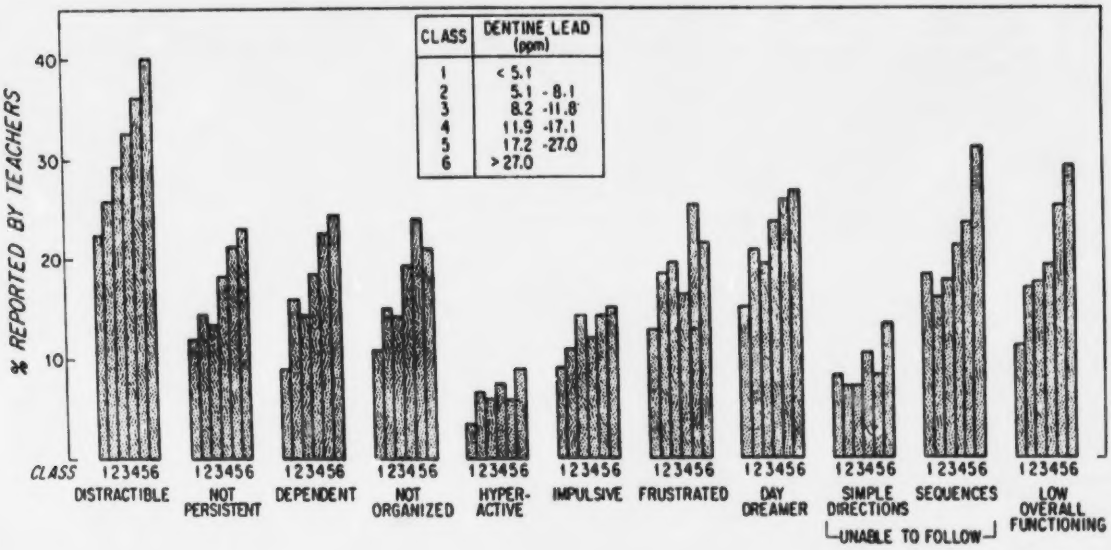
and low-lead groups. These variables were controlled in an analysis of covariance. Outcomes which differed between high and low-lead subjects are displayed in Table 1. High-lead subjects scored significantly lower on the WISC Full Scale and verbal IQ scores, on three measures of auditory and speech processing and on attention span at varying intervals of delay.

Table 1.

Outcome measure which differed significantly between high- and low-lead groups (ANACOVA).

WISC-R	Low Lead $\bar{X}$	High Lead $\bar{X}$	p Value (2-tail)
Full scale IQ	106.6	102.1	0.03
Verbal IQ	103.9	99.3	0.03
Performance IQ	108.7	104.9	0.08
Seashore Rhythm Test			
Subtest A	8.2	7.1	0.002
Subtest B	7.5	6.8	0.03
Subtest C	6.0	5.4	0.07
Sum	21.6	19.4	0.002
Token Test			
Block 1	2.9	2.8	0.37
Block 2	3.7	3.7	0.90
Block 3	4.1	4.0	0.42
Block 4	14.1	13.1	0.05
Sum	24.8	23.6	0.09
Sentence Repetition Test	12.6	11.3	0.04
Reaction Time Under Varying Intervals of Delay	($\bar{X}$ ± SD)	($\bar{X}$ ± SD)	
Block 1 (3 s)	0.35 ± 0.08 s	0.37 ± 0.09 s	0.32
Block 2 (12 s)	0.41 ± 0.09	0.47 ± 0.12	0.001
Block 3 (12 s)	0.41 ± 0.09	0.48 ± 0.11	0.001
Block 4 (3 s)	0.38 ± 0.10	0.41 ± 0.12	0.01

Figure 1. Teachers' Ratings of Classroom Behaviour in Relation to Dentine Lead Level. The height of each bar represents the percentage of negative reports for each lead group.



Examination of the teachers' rating scale for 2146 subjects showed a monotonic increase in poor scores in direct relation to the child's dentine lead levels (Figure 1).

Yule and associates (1981) studied English schoolchildren classified by blood lead levels. They reported that IQ and reading scores were significantly lower in high-lead subjects. In another study, the same group (Lansdown et al., 1983) applied the teachers' rating scale used by Needleman et al. (1979) in Massachusetts and found strikingly similar results. More recently, Yule's group (Yule et al., 1984) has employed the reaction time under varying intervals of delay, and reports similar increases with increasing blood lead levels. When the four curves from the two studies are superimposed, a striking dose-response relationship is observed (Figure 2). Smith (1985)

Figure 2. Comparison of Reaction Times at Varying Intervals of Delay in Subjects at Four Different Exposure Levels

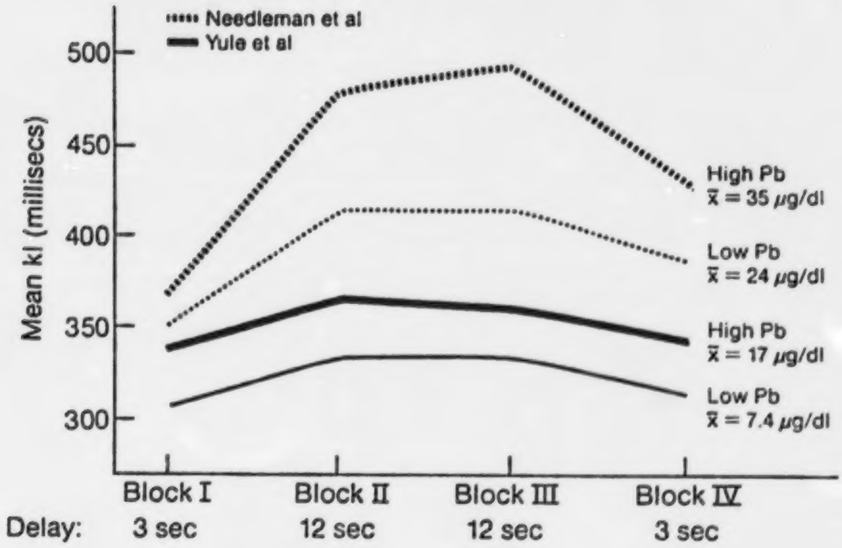
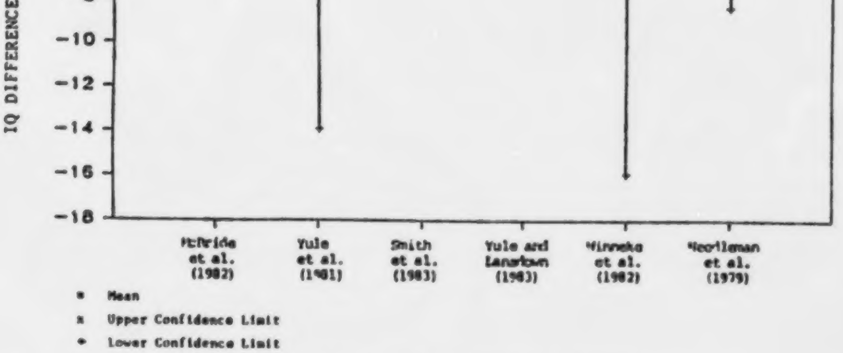


Figure 3. Mean IQ Differences Between High Lead Groups and Controls, adjusted for socioeconomic factors (90% confidence Intervals)



From: Costs and Benefits of Reducing Lead in Gasoline
US EPA/OPASS, March, 1984

studied a large group of London schoolchildren using dentine lead as the marker of exposure and controlled for a vast number of covariates. She found a statistically significant difference between groups prior to controlling for covariates. This difference decreased after entering covariates into the model, but continued to favour the low-lead group. Smith interpreted this study as indicating no effect, but there is not unanimous agreement with her interpretation. Winneke and associates (1983) found relationships between lead exposure and intellectual and behavioural functioning similar to those found in the Needleman study.

The Environmental Protection Agency Office of Policy Analysis (EPA), 1984) plotted the difference between IQ scores in high-lead groups and the confidence limits (Figure 3). It is clear that all studies conducted since 1979 show a difference favouring the low-lead group. Employing a meta-analysis, EPA calculated the probability that this result was obtained by a chance to be p = 0.005.

Lead crosses the placenta and can be found in the umbilical cord blood of infants in the delivery room. Rabinowitz and Needleman (1982) measured the umbilical cord blood lead of 11,837 Boston area infants over a 2-year period and found that the secular decline in levels measured on a monthly basis significantly correlated with the monthly sales of gasoline in Massachusetts (r = 0.75). Maximum correlation was obtained when umbilical cord blood lead lagged 1 month behind the scales of leaded gasoline. We evaluated the risks for low birth weight, low weight for gestational age and major and minor malformation for 4000 consecutive births in relation to their lead exposure. In this study, we controlled for socio-economic status and a number of other variables, including smoking, alcohol and drugs of abuse. Lead was found to be a strong predictor of the incidence of minor malformations. A dose-response relationship between risk for minor malformations and umbilical cord blood lead levels was found (Table 2).

Table 2.

Covariate-adjusted relative risk of malformation at selected blood lead levels.

Blood Lead Level (µg/dL)	Relative Risk*	No. of Neonates at Greater Lead Levels
0.7	1.0	98.7
6.3	1.87 (1.44-2.42)	50.0
15.0	2.39 (1.66-3.43)	1.7
24.0	2.73 (1.80-4.16)	0.2

* Mean ± 95% confidence interval.
Beta = 0.655 ± 0.273 (SE).

Interpretation

Review of the studies of low-level lead exposure and neuropsychological function to date converges on the finding that IQ scores, behavioural measurements and reaction time are impaired at levels of lead too small to bring the subjects to medical attention. Some investigators have evaluated the same group of studies and have concluded that no lead effect has been demonstrated or, if it has, that it is small in magnitude. This argument relies on a number of epistemic issues which deserve examination--they extend to many public health questions besides lead.

Among the reasons for the negative conclusions arrived at by some proponents are the following:

1) Endowing a p value of 0.05 with sacramental properties. Some investigators accept a significance of p = 0.06 or 0.08 as evidence that no effect has been found or, even more remarkably, that no effect exists. A given p value simply estimates the probability that the observed effect occurred by chance. There is reason to believe that the selection of 0.05 as a criterion of causal inference occurred because R.A. Fisher was granted copyright releases for only two lines in the table of p values: 0.01 and 0.05. Jerome Cornfeld's (1976) comment that the "prespecification of a significance level e.g., 0.05 or 0.01 has no sound logical basis and remains unjustified" is noteworthy in this regard.

2) Building non-veridical causal models. A number of authors attempting to avoid confounding have controlled in their analyses for as many variates as they could measure, without regard to where the variates fit in the causal pathway. This can result in overcontrolling and removing variance that properly belongs to lead. Winneke, for example, controls for "socio-hereditary" factors in his study, and finds that this reduces the variance due to lead. The socio-hereditary factor is a compound term consisting of father's type of employment (white or blue collar) and child's school placement (academic or vocational school). Because school placement is in part a result of school performance, this could be a lead effect, and removing it from the model would be expected to reduce the strength of the lead association. Variables should be positioned in the causal model on the basis of prior biological information.

3) Ignoring prior information. Many conclusions are drawn from studies considered in isolation without regard to other information gleaned from animal studies, from clinical reports of lead intoxication or from other

epidemiological investigations. As no study is without flaw, it is relatively easy to dismiss any given study on the basis of its own weakness, and then conclude that there is no effect while ignoring evidence from other reports which may respond to those questions previously raised. Animal studies, in which social factors can be precisely controlled by using litter mates and cross fostering, can address to some extent the issues of confounding due to social variables in human investigations. Animal studies also provide evidence for both plausible biological relationships and the presence of dose-response relationships. Deborah Rice's work (p. 247) presented to the Royal Society of Canada Commission on Lead in the Environment is pertinent in this regard.

4) Assigning shared variance exclusively to the control variable. In many circumstances, two variables are correlated and both have impacts on outcome. If the control variable is entered into the model first and the variance is reduced, many assume that this properly removes the amount of variance not attributed to the main effect. It may be that a substantial portion of this shared variance properly belongs to the independent variable. If lead and poverty are tightly collinear, and removing socio-economic status (SES) from the model reduces the size of the lead effect, it may well be that overcontrolling has biased the study towards the null.

5) Positing phantom covariates. Some have agreed that because the effect size is reduced when social covariates are entered, some unknown and unmeasured variable is the cause for the remaining difference. It is not necessary to look for ghosts in the epidemiological machinery.

6) Lack of statistical power. Many studies which report less than statistically significant effects of lead do not have sample sizes large

enough to find a significant effect if it were present.

These methodological issues are recurrent themes in the newer lead literature. The above criticism is not to be taken as an apology for lack of rigour. To the contrary, it acknowledges that epidemiological investigations occur in a crowded and complicated terrain in which variables and causal links do not sort themselves into linear arrays. Reduction of complexity through biostatistical modelling is necessary and, although scepticism about apparent relationships is appropriate scientific behaviour, Occam's Razor cautions us that it is not necessary, having looked with rigour and care for other interacting and potentially confound variables, to continue the seach indefinitely. If it looks like a duck and waddles and quacks it probably is a duck.

Conclusions

Regulatory agencies in the United States, Great Britain, Europe and Australia have defined neuropsychological effects in the population of children as the outcome most critical to the process of standard setting, and anchored their standards to preventing deficits in this group. The stakes, both hygienic and economic, can be seen to be huge, and contesting parties--those who have asserted that lead at low dose is dangerous and those who have asserted that it is not--have addressed the question with considerable force. This submission has attempted to review some of the more salient studies which bear on this issue including those by myself and my colleagues, to evaluate the scientific merit of these studies and to examine some of the epistemic positions which underpin the conclusions drawn by many of the investigators and critics.

If lead at low dose is a neurotoxic hazard of the seriousness suggested by most of the recent studies, why then has progress towards control of environmental sources been less than aggressive? At least part of the reason for this halting response has been the obdurate resistance of the lead industry to every regulatory action proposed by the government or by public health scientists. this is not a new state of affairs. In a recent review of lead regulation 60 years ago, Rosner and Markowitz (1985) showed that some health scientists warned as early as 1922 that alkyl lead gasoline additives were a serious health hazard. The government's response was to turn to the lead additive industry for the relevant toxicological data. The industry asserted that although no actual studies of toxicity were conducted, they were confident that a health problem did not exist. The US Government Bureau of Mines was commissioned to study the question, and editing rights over any reports issued were granted to the major producer of tetraethyl lead. The final report asserted that there was no risk from gasoline additives.

Recent attempts at environmental control of lead have been somewhat more even-handed. This has been because of the vigorous advocacy of public interest groups such as the National Resources Defense Council and the Environmental Defense Fund during the regulatory process. These agencies have been willing to enter the blurred area between science and politics, and represent the public interest in these proceedings. It is clear that the control of lead's neurotoxic potential will require the highest quality both of science and of transcientific public interest activity if the errors of the past are not to be reiterated at the expense of the developing nervous systems of children. The control of lead in the United States has been a slow and arduous process. I trust the proceedings of this Society will spare Canada from unnecessary delays in protecting its citizens from this toxicant.

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13. IMPLICATIONS OF CURRENT LABORATORY FINDINGS FOR ASSESSING THE HUMAN HAZARDS OF ENVIRONMENTAL LEAD

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Contemporary research on the behavioural toxicity of lead can be dated from the mid-1960's, when Pentschew and Garro (1966) described their neonatal model. Until then, in contrast to the cogent human literature, animal research seemed unrewarding, even frustrating. Common laboratory species, such as rodents, provided little evidence of sensitivity at exposure levels anywhere comparable with those producing adverse effects in humans. Pentschew and Garro, by demonstrating neurotoxicity in rat pups exposed through maternal milk, provided a model that, since then, has dominated experimental work. Only recently, however, has animal research begun to yield data that enlarge our understanding of the scope and problems of human toxicity.

Three factors underlie this lag between the earlier efforts and their applications to hazard assessment, as noted by several extensive reviews (Michaelson, 1980; Bornschein et al., 1980; Cory-Slechta, 1984). One was the absence of measures of dose and the absence of dose variation. Many of the earlier studies did not appreciate the role that measures of exposure, such as blood concentrations, play in toxicology. Many seemed unaware of how much reliance toxicology places on the dose-response (or dose-effect) function to validate the choice of end-point and to guide the pursuit of mechanisms.

A second factor, surely related to the first, was the choice of exposure levels so extreme that overt toxicity ensued. Weight loss or retarded weight gain, the most common consequence, was confounded with the more specific effects of lead exposure. Michaelson's review centred on this confounding, and pointed out that almost every effect ascribed to lead neurotoxicity had also been demonstrated in animals subject to undernutrition alone. He also demolished the argument that high doses, despite these problems, help indicate mechanisms.

The third factor was the choice of behavioural end-point. Some investigators, attracted by claims that excessive lead exposure could induce the syndrome of 'hyperactivity' in children, adopted motor activity in rodents as analogous, failing to note that the clinical syndrome embraced far more than activity. Such studies produced a confusing body of data, as noted by Bornschein et al. (1980). Some investigators, perhaps because of unfamiliarity with the literature of behavioural pharmacology, reached backward into the behaviour science of the 1930's, and spent countless hours training rats to navigate mazes.

Despite this disappointing history, however, an increasing awareness of these issues has become manifest among experiments during the past few years. It has produced a literature much more pertinent to the issues framed by this Commission. And it indicates that the cumulative evidence from epidemiological research, which suggests adverse consequences from relatively mild elevations of lead exposure, points in the proper direction.

I find the clearest, most cogent and most consistent evidence in those experiments framed around operant, i.e. schedule-controlled, behaviour. These terms refer to an experimental situation in which a specified behavioural act, such as pressing a lever in a specially designed chamber, is maintained by following specified occurrences of the act with an event such as the delivery of a small pellet of food. Such contingencies, as they are called, yield reproducible behavioural baselines with two crucial advantages. One is that they test the organism's capacity to deal with complex environmental demands, in much the same way that its survival in the natural environment depends upon its making optimal foraging choices. In fact, schedule-controlled behaviour is now being studied by economic models. The second advantage is the ability to exploit multiple indexes of performance in a single situation in which performance stability makes it possible to trace the gradual unfolding of a chemically modified process.

Until quite recently, animal laboratory research on lead seemed somewhat remote from the issues provoked by epidemiological findings. Newer evidence, however, benefitting from a 20-year refinement of methods and approaches, is now yielding a cogent perspective on such issues. The control over extraneous and confounding variables offered by current laboratory research suggests that even the revised definition of risk levels proposed by the US Centers for Disease Control may be insufficiently rigorous. Experiments conducted at Rochester and elsewhere indicate that in an allegedly resistant species, the rat, and even at a stage of the life cycle -- after weaning -- presumed to be less vulnerable than the neonatal period, blood concentrations of 10-20 µg/dL produce behavioural aberrations. Such data are consistent with those gathered from monkeys in an elegant series of studies conducted by Rice and her colleagues in Ottawa (p. 247). These primate data demonstrate that blood lead levels as low as 10-15 µg/dL are associated with a wide spectrum of behavioural dysfunctions, many of which are strikingly similar to those observed in children with elevated lead burdens. Moreover, there is no compelling evidence that even these levels represent a threshold range.

The consistency of these laboratory findings argues that the newer epidemiological data, suggesting behavioural deficits in the same range of blood levels, are valid. The implications are disquieting. They indicate that an increment of about 10 μg/dL, as from 10 to 20 μg/dL, is associated with a population decrement in IQ scores (only one of the adverse consequences) of about 5 points. For a nation of 20 million, it means a reduction in the number of persons with scores above 130 from about 460,000 to about 198,000, a 60% reduction. Advanced industrial societies cannot afford to ignore such a threat to their competitive positions.

Surveying what has been accomplished so far yields the following conclusions:

1) Blood lead levels as low as 15-20 μg/dL significantly alter behaviour in rats, even those treated by exposure through drinking water after weaning, when susceptibility is alleged to be lower than during the neonatal period.

2) Even in a homogeneous group of rats, the response to lead treatment displays wide individual differences. The usual group statistics do not reflect such differences, and are surely even more misleading in human studies.

3) The choice of behavioural end-point is critical. Behaviour is not a unitary phenomenon, like blood pressure, but one with multiple facets that do not lend themselves to a single number.

These conclusions, moreover, do not stand alone. Studies by the Cincinnati group, by experimenters in Europe and by Rice and her colleagues in Canada point to similar conclusions.

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14. BEHAVIOURAL EFFECTS OF DEVELOPMENTAL LEAD EXPOSURE IN MONKEYS

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For the past decade, the Health Protection Branch has been studying the health effects, including behavioural effects, of lead exposure from birth onward in the monkey (Rice and Willes, 1979). Although lead intake in the lowest dose group of this study is approximately 5- to 10-fold greater than estimates of lead intakes by children, doses of lead were chosen to result in blood levels typical of those observed in children. For all three treated groups, blood lead concentrations rose from birth to 100 days of age, were stable for about 100 days (to 200 days of age) and then declined to steady-state levels which then were constant (the oldest monkeys are now about 10 years old). This observation respecting the rise and decline of blood levels is comparable with that observed in the human population. The highest dose group has blood lead concentrations that are considered by most investigators to produce intellectual impairment and/or behavioural disorders, whereas the lower dose groups are representative of the blood lead levels observed in most children (Table 1).

It is now recognized that blood lead levels are poor indicators of body burden of lead (i.e. as opposed to good indicators of recent exposure) and that they therefore cannot *ipso facto* be used to assess the hazard posed by lead. In other words, except under controlled conditions, the steady-state blood lead level cannot be correlated with past lead exposure which may be responsible for untoward effects including behavioural effects. Nevertheless, blood lead levels do serve in a qualitative manner as indicators of lead exposure. Ten years ago when we started the study, blood lead levels were utilized to define 'safety', and blood lead levels observed in our two lower dosed groups were considered safe for children. Over the past 5 or 6 years it has become increasingly apparent, from both animal and human studies, that even at such blood lead concentrations behavioural impairment is observed. Reprints (or preprints) of much of the work from our laboratory have been made available to the Commission. The present report will concentrate on interpretation of effects found at the lower doses, and comparison of these data with findings in children.

Table 1.

Mean blood lead levels early in life (peak) and at steady-state conditions.

Dose (µg/kg/day)	Peak: Mean + SE (µg/100 mL whole blood)	Steady State: Mean + SE (µg/100 mL whole blood)
0 (control)	2.2 + 0.4	3.4 + 0.8
50	15.4 + 1.7	10.9 + 0.7
100	25.4 + 2.0	13.1 + 1.4
500	55.3 + 6.7	32.8 + 5.3

Specific Behavioural Tests in Monkeys

The first task that the monkeys were tested on, as 3-year-olds, was an intermittent schedule of reinforcement--the fixed interval (FI). (See Rice and Willes (1979) for details of the procedure.) This task in some ways may be considered a measure of the activity of the monkey, but is more precise than simply measuring locomotion, for example. It was found that lead-treated monkeys made more responses per unit time (were more active) than control monkeys, in a dose-dependent manner. These data are consistent with effects found in rodents, at approximately the same blood levels (Weiss, p. 241).

The next task the monkeys were tested on was another intermittent schedule of reinforcement, the differential reinforcement of low rate (DRL) (Rice and Gilbert, 1985). This task required the monkey to learn to inhibit responding by requiring a minimum time between responses for reinforcements. However, the monkeys were retarded in their ability to learn to inhibit responding compared with controls, in a dose-dependent manner. When all the monkeys had learned the task, the consistency of performance was examined by measuring the day-to-day variability for each monkey. The treated monkeys behaved in a more inconsistent manner from day to day, again in a dose-dependent manner. This has been a universal finding in our laboratory, and one which is even more marked at higher doses than those discussed in this report; lead-exposed monkeys are more changeable in their behaviour from day to day, or even within a few minutes, than are control monkeys (Rice, 1985b).

The monkeys were next tested on a discrimination reversal task. This task assessed the monkeys' ability to adapt to changing 'rules'. Once the monkey learned a task, the requirement changed so that the opposite answer was correct. This discrimination reversal was performed a number of times, for three different tasks (Rice, 1985a). It was found that treated monkeys were retarded in their ability to learn to adapt to changes in requirements made of them. These results at lower doses confirmed results from monkeys with higher blood lead levels (Rice and Willes, 1979; several University of Wisconsin reports).

These monkeys, now adults (7-8 years old), have recently been tested on a spatial alternation task. It required the monkey to alternate responding between two buttons, with no external cue to indicate the correct response. Initially the delay required between responses was very short, and was lengthened over the course of the experiment to a final value of 15 s. Treated monkeys were initially impaired in their ability to learn the task, but ultimately were able to learn the task as well as controls. At long delay values, they made more errors than controls, responding on the same button in some cases for hours at a time. The results were consistent with an attention and/or memory deficit. A similar finding had been observed in the higher-dose group on a different task (Rice, 1984).

Comparison with Behavioural Effects in Humans

At steady-state blood lead levels between 11 and 13 μg/dL (peak early in life of 15-25 μg/dL), monkeys exhibited higher activity, impaired learning, impaired ability to learn to inhibit unwanted activity, inconsistent behaviour, impaired ability to adapt their behaviour to changing requirements imposed on them and attentional/memory problems. These effects have also been observed in rodents and monkeys by other investigators, at similar or higher blood lead levels. Moreover, it appears that the biochemical effects of lead in the monkey, such as elevation of free erythrocyte protoporphyrin (15-18 μg/dL) and inhibition of δ-aminolaevulinic acid dehydratase (10 μg/dL), occur at the same blood lead concentrations as in children. This, combined with the fact that the nervous system and development of the monkey is remarkably similar to those of the human, indicates that the developing monkey is an appropriate model for studying the effects of lead in children.

The evidence collected in the last several years points to the fact that relatively low body burdens of lead can result in deficits in IQ in children (EPA, 1985). This is consistent with the impaired learning ability observed in animals, in both our laboratory and others.

Other behavioural effects of lead observed in our monkeys are also consistent with those reported for children with moderate body burdens of lead. Needleman's Teacher Questionnaire (Needleman et al. 1979) found that elevated tooth lead resulted in such behaviour as increased distractibility, decreased

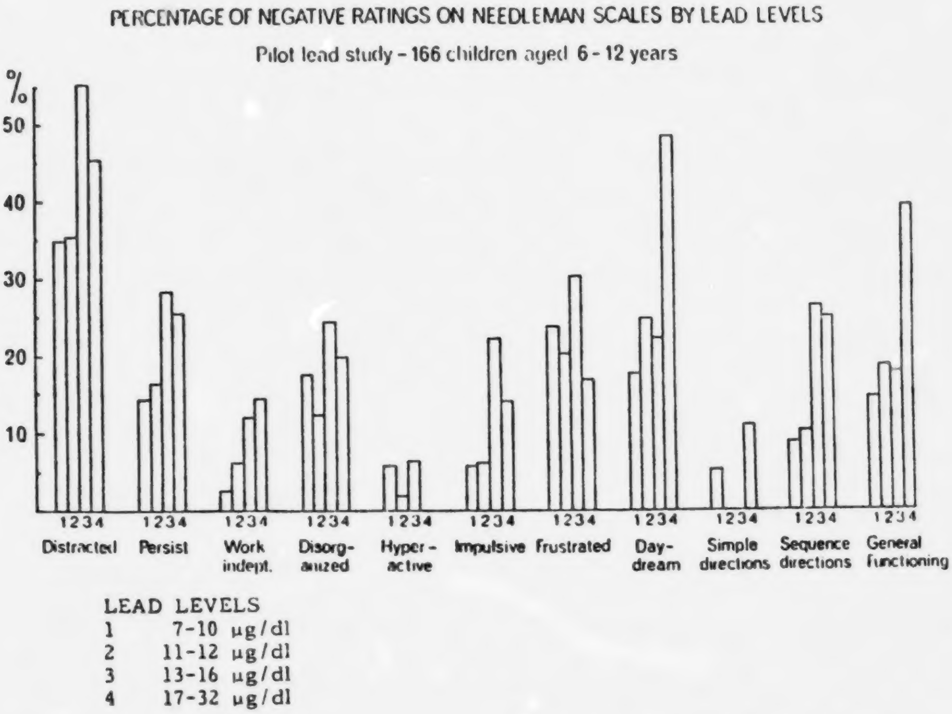
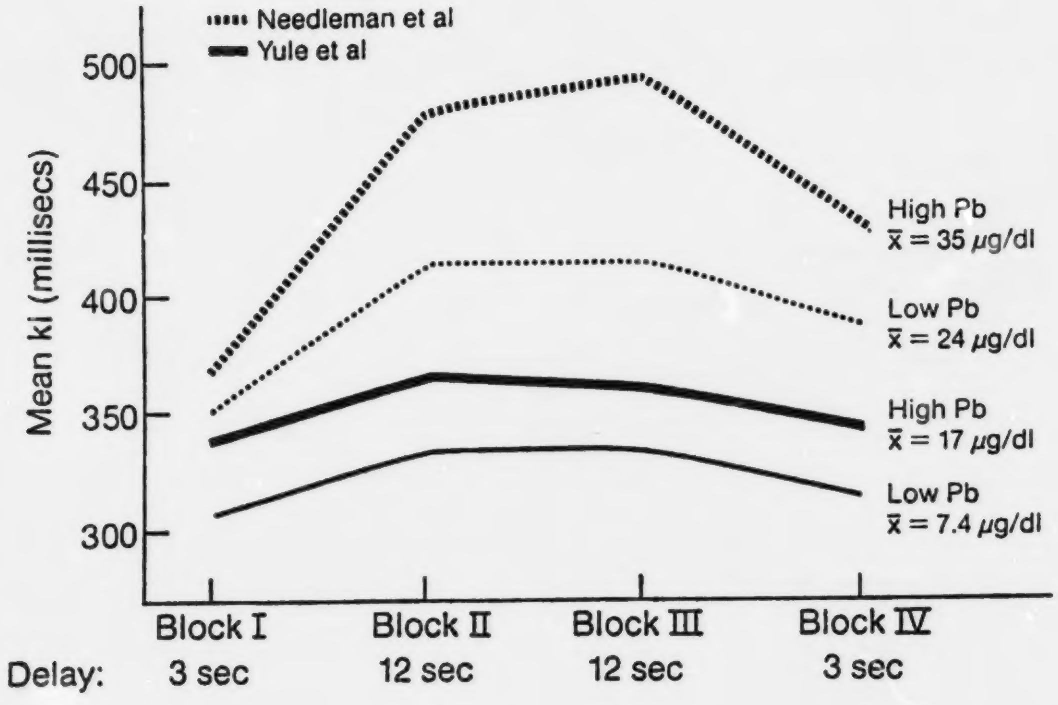


Fig. 1. Percentage of negative ratings on Needleman scales by lead levels Pilot lead study - 166 children aged 6-12 years.

organization, hyperactivity, impulsive behaviour, inability to follow simple and complex directions and low overall functioning in a classroom setting (Figure 1). These findings were replicated by Yule et al. (1984) in British children having lower body burdens of lead (Figure 2). These descriptions of child classroom behaviour match extremely well with the finding in our monkeys of increased activity, inability to inhibit unwanted responses, inconsistent behaviour and inability to follow 'rules' of a task.

Figure 2. Comparison of Reaction Times at Varying Intervals of Delay in Subjects at Four Different Exposure Levels



Both Needleman et al. (1979) and Yule et al. (1984) also tested the ability of lead-exposed children to pay attention for a relatively short period of time. They asked the child to release a button upon hearing a tone. When the time between the word 'Ready' and the onset of the time was increased, children with higher lead exposure performed relatively more poorly; their performance also deteriorated more over the course of the 20-min test than did that of children with lower body burdens. Moreover, there was a clear dose-effect relationship (Figure 2). This can be interpreted as an attentional deficit, which would obviously make it difficult for the child to do well in school. Again, we have data from monkeys that suggest a deficit in attention.

In summary, it is clear that various kinds of behavioural impairment are observed in the monkey at blood lead concentrations that are observed routinely in the general population of children. It is equally clear that similar sorts of impairment are observed in children with elevated body burdens of lead. The most parsimonious explanation of these findings is that lead is neurotoxic to the developing child, and that one cannot dismiss the observations made to date concerning the impact of lead on behaviour in children. Furthermore, blood lead levels cannot be relied upon without a very extensive study of the time-related exposure patterns to assess potential hazard or establish safety.

Further work is planned to establish a better correlation between the results observed in monkeys and those in children. For example, a comparison of tooth lead in monkeys with that observed in children might prove a more interpretable indicator of relative body burden. In addition, further comparison of biochemical effects of lead on monkeys and children would serve to strengthen the confidence of extrapolation between the two species.

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15. NEUROBEHAVIOURAL EFFECTS OF LEAD: A SUMMARY REVIEW OF CROSS-SECTIONAL AND LONGITUDINAL STUDIES

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There is a general consensus that high levels of lead exposure. in utero and during early childhood, can often lead to serious, even fatal, sequelae. There is increasingly less consensus regarding the character and/or existence of neurobehavioural effects as one examines the literature pertaining to progressively lower levels of lead exposure. This is the case because we are moving down on the dose-response scale from the realm of a pure main lead effect toward a region in the dose-response scale where lead's effects are less discernible relative to other factors which influence child development. behaviour and performance. In fact, it is possible that 'lead effects' at low exposure levels occur only as a result of interaction with other insults. For the purpose of this review, the history of neurobehavioural lead research has been divided into several phases.

Pre-1979: Cross-sectional, Retrospective Studies

Studies during this era, although often state-of-the-art at the time they were undertaken, are crude by today's standards. This literature has been subjected to frequent and thorough review (Bornschein et al., 1980; Department of Health and Social Security, 1980). Clear-cut interpretation of the findings from these studies is hampered by their numerous methodological flaws. For example, lead exposure histories were poorly documented. Frequently, only a single recent blood lead value at the time of behavioural testing, was used, leading to poor separation between high-lead and low-lead exposure groups. Other unreliable indices of lead exposure history have also been used, e.g. hair lead concentration.

Often no rationale was given for the selection of neurobehavioural tests used to index lead's posited effect on behaviour or cognition. This resulted in too many tests being administered, with an increased likelihood of incurring a false-positive finding. The use of insensitive tests increased the chance of false-negative findings, whereas the use of non-standardized and/or subjective tests led to difficulties interpreting the studies' findings.

Although these studies did little to resolve the question of whether or not lead causes neurobehavioural deficits at low levels, they did result in a heightened awareness of a potentially serious health hazard and the need for well-designed and well-executed epidemiological studies of the etiology of poor neurobehavioural outcomes in school-age populations.

1979-1983: Retrospective Studies

The first of a new generation of studies which attempted to avoid the problems of the earlier studies was that of Needleman and his colleagues (Needleman et al., 1979; Needleman and Landrigan, 1981). This study and those of five other research groups have been critically reviewed (Rutter, 1980. 1983; EPA, 1984; Harvey, 1984; Harvey et al., 1984; Smith, 1985; Yule and Rutter, 1985). Key aspects of these studies are summarized in Table 1 taken from Smith (1985). The results of the psychometric findings are summarized in Figure 1. The mean full-scale IQ difference between the high- and low-lead exposure groups, as well as the 90% confidence interval for the estimate of the mean difference, is shown for each of the major reported studies. If the 90% confidence interval does not include zero (e.g. Needleman et al., 1979;

Table 1.

Studies reviewed (Smith, 1985)

First Author	Date of Publication	Location of Study	Age of Subjects (yr)	N Sample/Type Sample	Primary Lead Measure	Lead Levels	Summary of Tests in Test Battery	Behavioural Measure	Covariates Controlled
Needleman	1979	Massachusetts (US)	7-8	158 (groups), 58 high, 100 low	Tooth: dentine slice	Mean PbT, <10 μg/g or >20 μg/g	WISC-R: Educational Attainment; Auditory and Languages Processing; Visual-motor Competence; Attentional Performance; Motor Coordination	Teachers: 11-item forced choice scale (Needleman)	Father's SES, mother's age at child's birth, number of pregnancies, mother's education, mother's picture vocabulary score
Winneke	1979	Duisburg (Germany)	7-10	52 (26 matched pairs)	Tooth: whole incisor	PbT, <3 μg/g, >7 μg/g	German WISC: Visual Motor Integration; Gross Motor Coordination	Observational based on Conners' Scale	None--groups matched on on father's SES
Winneke	1983	Stolberg (Germany)	7-12	116 (continuous range)	Tooth: whole incisor	PbT, 1.5 μg/g to ~38 μg/g	German WISC: Visual Motor Integration; Vienna Reaction Device	Mother and teacher on standardized 7-item scales	Duration of parturition, socio-hereditary background
Yule	1981	London (UK)	6-12	166 (treated as quartiles for analysis)	Blood	PbB 7-32 μg/dL (7-10, 11-12, 13-16, and 17-32 μg)	WISC-R: Educational Attainment	Teachers: Conners' scale; Needleman Rating; Rutter scale	Father's social class (not behavioural measure)
Thatcher	1982	Maryland (US)	5-16	149 (continuous range)	Hair	PbH, ≈4-28 ppm; mean ≈14.5 ppm	WISC-R: Educational Attainment; Fine and Gross Motor Movement		SES
McBride	1982	Sydney (Australia)	4-5	200 (2 groups)	Blood	PbB, ≤9 μg/dL or ≥19 μg/dL	Picture Vocabulary Test; Fine and Gross Motor Coordination	Mother: Rutter Scale	None
Smith	1983	London (UK)	6-7	403 (3 groups)	Tooth: whole incisor, crown	PbT, ≤2.5, 5-5.5 or ≥8.5 μg/g	WISC-R: Educational Attainment; Verbal and Auditory Performance; Visual Attention and Memory; Coordination and Neurological Examination	Mother and teacher: Conners' Scale	Mother's IQ, parental interest, family characteristics; quality of marital relationship, mother's mental state, parental education
Harvey	1983	Birmingham (UK)	2½	189 (continuous)	Blood	PbB, 6-28 μg/dL	British Ability Scales; Cognitive and Psychomotor ability; Developmental scales	Observational: structured rating of play session	Father's social class and educational level; life events; mother's age, general health questionnaire score; marital satisfaction; child's birth order; pica
Yule	1983	London and Leeds (UK)	6-12	194-302 (treated as quartiles for analysis)	Blood	PbB, 7-24 or 5-26 μg/dL; mean 11.8 μg	WISC-R: Educational Attainment	Mother and teacher: Rutter and Needleman Scales plus Teacher Conners' Scales	(Analysis not completed)

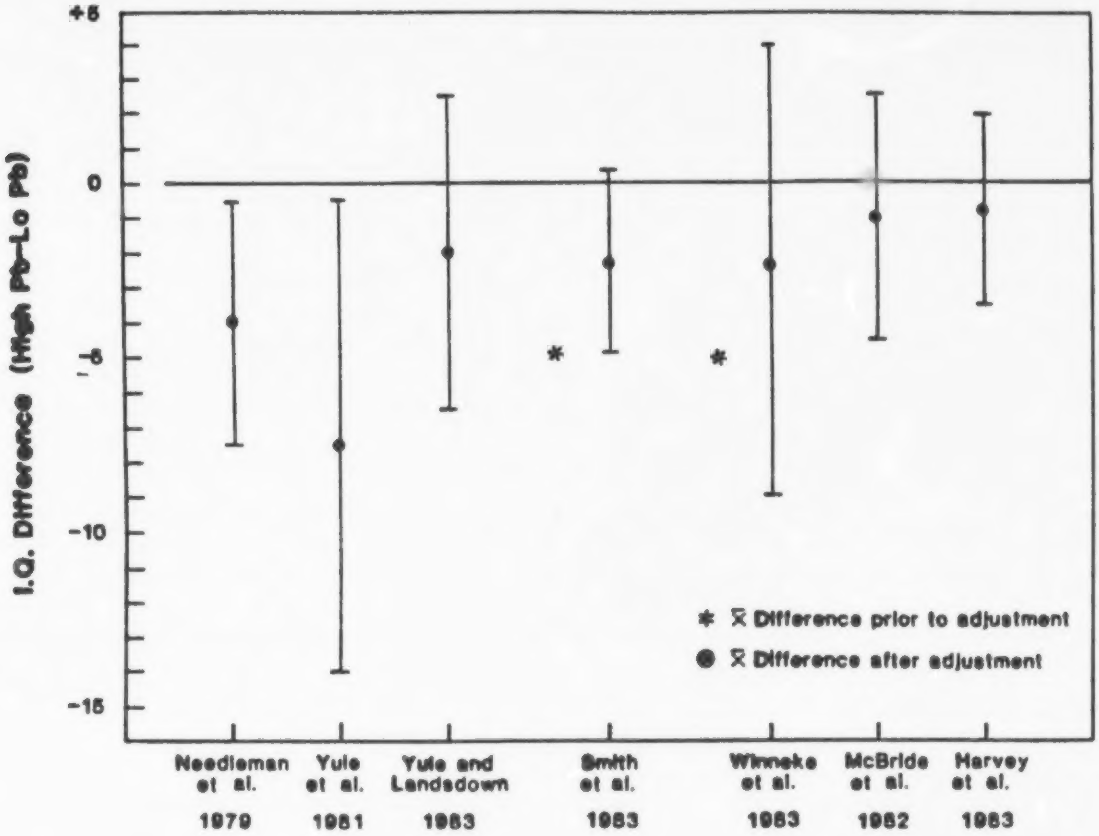

FIGURE I

Mean IQ Difference Between High Lead Groups and Controls, Adjusted for Socioeconomic Factors (90% Confidence Intervals)

Yule et al., 1981), then this is interpreted as the graphic equivalent of detecting a significant effect at p less than 0.05. Two studies (Smith et al., 1983; Winneke et al., 1983) found mean differences of about 5 IQ points prior to adjustment for covariates and confounders. However, after statistical adjustment, these differences were reduced to about 2.5 IQ points and were no longer statistically significant. Much has been made of the fact that even though the majority of these studies have not found statistically significant lead effects, the effects are all in the hypothesized direction, i.e. high-lead exposure groups performed more poorly than the low-lead exposure groups (EPA, 1984). There is general agreement that before controlling for social factors there is an association between higher exposure levels and poorer performance on psychometric tests. It is also generally agreed that after statistical adjustment the size of the group effect is reduced to an average of about 2.5 IQ points for the studies in question. However, there is considerable controversy about the appropriateness of the statistical adjustment and the interpretation of why it results in a reduction in the size of the apparent lead effect. Many argue, on good grounds, that blood lead elevations are serving as a marker for social disadvantage, i.e. that they are highly correlated (Milar et al., 1980). If so, then the IQ deficits could be due to social disadvantage and not lead. Many further argue that if the child's social environment could be more accurately measured, then the apparent association between lead and IQ would disappear completely. Others have raised the equally valid concern that the inclusion of numerous highly intercorrelated social factors into the regression analyses can result in statistical overcontrol and in an underestimate of the true size of lead's effect. This debate can not be resolved through interpretation of the published papers. What can be concluded at the present time from existing published studies is as follows:

1) There are no substantial data yet available that support the contention that low-level lead exposure is causally associated with behavioural disorders such as hyperactivity or attention disorders. Further studies with measurement techniques other than questionnaires are needed.

2) There is good evidence for a positive association between level of lead burden and degree of social disadvantage.

3) Prior to statistical adjustment for social covariates, there is a negative association between lead burden and IQ.

4) After statistical adjustments for social factors have been incorporated into the analyses, the lead/IQ relationship is substantially reduced and is usually not statistically significant.

5) If there is a causal association between low-level lead burden and IQ. it is quite small. The shared variance between lead burden and IQ is about 5%. and the size of the lead effect on group IQ is about 2.5 IQ points. This is very small relative to other factors known to influence IQ.

6) If a causal link exists it is most likely to be observed among socially disadvantaged children, where the lead effect interacts with other developmental adversities.

7) There is as yet no strong evidence that low-level lead exposure constitutes a universal hazard to all children.

Further resolution of this issue awaits new cross-sectional studies which incorporate further refinements in methods of behavioural assessment. To this end, the World Health Organization is co-ordinating the execution of five new cross-sectional studies throughout Europe (Farkas et al., 1984).

This co-ordinating effort is under the direction of Dr. Gerhard Winneke of the University of Düsseldorf. The groups are utilizing a common research protocol. Results will be forthcoming in 1986. The levels of lead exposure being observed in these studies are likely to be more comparable to those encountered in Canada today than those reported in United States studies during the late 1970's.

1979-Present: Longitudinal Studies

Recognizing the limitations and interpretative difficulties of cross-sectional, retrospective studies, several research groups have undertaken prospective, longitudinal studies. Preliminary, interim reports are now appearing in the literature or being reported at scientific meetings. The research protocols and description of cohorts being followed have been reported (Bornschein, 1981; Bornschein and Rabinowitz, 1985).

A brief synopsis of early, interim results follows:

1) Boston Study--This longitudinal study of 249 infants has yielded results suggestive of an effect (not always negative) of pre-natal lead burden on the indices of minor physical anomalies and other indices of morbidity. It also reports a negative association between lead burden and 12-month Bayley mental development index (MDI) scores. No association between post-natal lead burden and Bayley MDI scores has been reported (Bellinger et al., 1984).

2) Cincinnati Study--These investigators are studying a cohort of over 300 children. The cohort is subjected to a wide range of lead exposure levels and experiences a range of social adversities. An interim analysis finds a significant negative association between pre-natal blood lead (PbB) level and duration of gestation, as well as birth weight after controlling for appropriate covariates, including duration of gestation. A negative association

between indices of pre-natal lead exposure and Bayley mental and motor scales at 6 months of age has been observed. No effect of post-natal indices of exposure are related to 6-month Bayley scales after controlling for pre-natal exposure (Dietrich et al., 1985). In fact, early post-natal lead exposure appears to be positively associated with and perhaps due to rapid motor development (Dietrich et al., 1985).

3) Cleveland Study--Preliminary results on about 150 infants suggest a negative association between cord blood lead levels and neonatal neurological status. However, no direct association between cord PbB level and later Bayley MDI scores at 24 months was apparent.

4) Glasgow Study--This study involves the longitudinal follow-up of 150 infants of mothers exposed to various levels of lead in drinking water during pregnancy. It found lower birth weight with increasing maternal PbB level and an increase in length at birth. Performance on the Bayley mental and motor tests at 12 months was associated with birth weight, father's social class and home environment, but not post-natal lead exposure.

5) Port Pirie Study--These investigators followed the outcome of over 800 pregnancies in a community surrounding the world's largest lead smelter. They reported a significant positive association between lead burden and preterm delivery which remained statistically significant when a variety of other potentially confounding variables were taken into account. They also reported a negative association between Bayley MDI scores at 24 months and several indices of post-natal lead burden. This effect remained after controlling for several covariates and confounders, but pre-natal lead burden was not controlled.

The longitudinal studies appear to be finding an effect of in utero lead exposure on birth weight and very early performance measures. Conversely, these studies have not yet demonstrated any effects of post-natal lead exposure. The long-term consequences of these exposures await maturation of these cohorts.

Electrophysiological Studies

In addition to behavioural and cognitive assessments in children, there are a limited number of studies which have examined the association between lead exposure and central nervous system (CNS) function as indexed by electrophysiological changes (Otto et al., 1982; Winneke et al., 1984). These early studies which purport to demonstrate lead neurotoxicity at very low levels of exposure have repeated many of the same errors pointed out previously for the early cross-sectional retrospective behavioural studies. Absolutely no conclusions can be reached regarding the effects of lead on the electrophysiology of the CNS. Otto, Winneke and others do have new studies about to be initiated which should result in interpretable findings.

Consequences of Early Neurotoxic Insult

If one assumes that foetal and/or infant lead exposure results in a measurable, reproducible deficit in performance on tests such as the Bayley Scales, what can be said of the long-term consequences with regard to school performance and other indices of social and academic competency? Obviously, cross-sectional studies, with assessments administered at a single point during the course of development, cannot answer such a question. The current longitudinal lead studies will ultimately address this issue; however, these cohorts are still of pre-school age. It is possible, however, to gain insight into the range of possible outcomes by viewing the results of other longitudinal studies of early CNS insult (Winneke et al., 1985; Rutter, 1983). Neuro-toxins are often viewed as having a deleterious effect on development regardless of the constitutional vulnerability or robustness of the child or the quality of the home environment in which the child develops. Although this is undoubtedly true under conditions of very high exposure, it is less likely to be the case at lower levels of exposure. Recent research in the field of foetal malnutrition has demonstrated the inaccuracy and inadequacy of such a concept (Zeskind and Ramey, 1981) (see Table 2). This study consisted of the random assignment of foetally malnourished (low ponderal index) and control infants drawn from a low social-economic status (SES), black population, to environments differing in quality of support for intellectual development. They found that the detrimental effects of foetal malnutrition persisted and became progressively worse in 36-month-old infants reared in a non-supportive environment (General Cognitive Index = 71 ± 10). Those high-risk infants receiving additional stimulation exhibited intellectual performance (96 ± 11) considerably above those not receiving environmental intervention (71 ± 10) and performed at a level comparable with those of infants not at risk and receiving additional stimulation (98 ± 14). Thus, the developmental trajectory of infants subjected to various environmental insults is not determined solely by the nature of the insult. It is subject to modification by the child's subsequent interactions with his/her environment. Contrary to the belief of some, a child's cognitive ability as reflected in performance on IQ tests is not a static biological entity but, rather, it is highly labile and subject to the quality of rearing environment. Thus it is highly likely that the outcome of any lead insult incurred during infancy will be shaped by the child's social environment, thereby producing a wide spectrum of performance by the time the child reaches school age.

Table 2.

Influence of foetal malnutrition and caregiving environment on intellectual development of infants (Zeskind and Ramey, 1981).

Ponderal Index*	Infant Stimulation	Age (months) 3**	18**	36***
Average	Yes+	102	107	98 ± 14
	No	97	93	84 ± 10
Low	Yes	92	104	96 ± 11
	No	91	86	71 ± 10

* Ratio of weight to height at birth; used as an index of foetal nutrition.

** Bayley Mental Development Index Scores.

***McCarthy General Cognitive Index Scores (normal = 100 ± 15).

+ Daily participation in a daycare infant stimulation programme.

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16. THE NEUROBEHAVIOURAL EFFECTS OF PRE-NATAL AND EARLY POST-NATAL LEAD EXPOSURE: AN INTERIM REPORT FROM THE CINCINNATI LONGITUDINAL STUDY

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Studies of the neurobehavioural effects of low to moderate childhood lead exposure have yielded equivocal results (Bornschein et al., 1980). Some reviewers have concluded that such inconsistent findings reflect the retrospective/cross-sectional nature of previous investigations (i.e. poor documentation of dose and/or behavioural development) and inadequate statistical control of biological and social covariables which may mimic or obscure the health effects of lead (Rutter, 1980; Pearson and Dietrich, 1985). It has been argued that a longitudinal design is the minimum basic requirement for the reliable estimation of toxic dose, and for estimation of the relative effects of lead exposure which may be confounded with other potent developmental influences. A prospective methodology also presents the opportunity to assess changes in vulnerability to lead with age , and the reversibility of adverse neurobehavioural response to exposure (WHO, 1971). This view has encouraged the initiation of several well-designed prospective investigations into the health effects of childhood lead exposure in the United States, Europe and Australia (Bornschein and Rabinowitz, 1985). The Cincinnati Longitudinal Study is one of these.

Although previous researchers have focussed on the school-age child, there is some reason for concern about the acute and long-term effects of foetal and infant lead exposure. The foetal and infant periods are obviously critical to adequate central nervous system structure and function. Delays in the accumulation of cerebral cytochromes and cerebral cortical synaptogenesis have been linked to pre-natal lead exposure in animal studies (Bull et al., 1979; McCauley et al., 1979, 1982). Metabolic balance studies have shown that young animals and human infants absorb and retain a higher percentage of total ingested lead than adults (Alexander et al., 1974; Ziegler et al., 1978), and there is considerable evidence that the placenta is a poor physiological buffer for lead (Angle and McIntire, 1964; Angell and Lavery, 1982). Further, lead has known or highly suspected biological effects in infants and children such as increased erythrocyte protoporphyrin (Piomelli et al., 1982; Hammond et al., 1985), and depression of 1,25-dihydroxycholecalciferol (Mahaffey et al., 1982). One study even suggests that low-level foetal lead exposure may increase the probability of minor congenital anomalies (Needleman et al., 1984). However, this study did not find an association between low-level lead exposure and more significant biological risks such as decreased birth weight, shortened gestation, Apgar score or respiratory distress.

The literature on the early neurobehavioural effects of lead exposure in human infants is meagre. Well-designed prospective studies initiated during the last few years have only recently issued preliminary findings. Bellinger et al. (1984) recently reported an inverse association between umbilical cord blood lead levels and 6-month covariance-adjusted scores on the Mental Development Scale of the Bayley Scales of Infant Development (Bayley, 1969). Post-natal blood lead levels at 6 months were unrelated to behavioural development as measured by the Bayley Scales. The Bayley Scales yield a Mental Development Index (MDI) which, at 6 months, reflects the infant's attentiveness and responsiveness to stimuli, rudimentary problem-solving and display of early precursors of communicative behaviour. Whereas such 'developmental quotients' are poor predictors of later childhood IQ, they are good contemporaneous indicators of neurological intactness (Ulvund, 1984).

The finding of a significant negative relationship between cord blood lead (coded categorically as low, medium and high) and MDI seems both surprising and alarming, given the apparently low levels of foetal exposure in the Bellinger et al. (1984) study. This study reported mean cord blood lead levels in the low, medium, and high groups of 1.8, 6.5, and 14.6 µg/dL, respectively. Also surprising is the fact that effects were found in a study sample which was predominantly white and middle to upper-middle class--a sample at relatively low risk for developmental delay. However, the negative parameter estimate for cord blood lead effect on Bayley MDI, although statistically significant, was quite small ($B = -2.89$). A change of 2.89 MDI points can amount to only 1, or even a mere fraction of a single item on the Bayley Mental Development Scale. The average number of scale items administered to a single 6-month-old infant is around 50 ± 6. Thus, the psychological meaning of the Bellinger et al. (1984) results is difficult to fathom. Nevertheless, this study does suggest that, even within a low-risk sample, low-level foetal lead exposure has an effect, albeit small, on early sensorimotor development.

Moore and colleagues (Moore et al., 1982; Moore and Bushnell, 1984) examined the relationship between maternal blood lead concentration, assessed during the first trimester of pregnancy, and Bayley MDI scores at 12 and 24 months. Study subjects were divided into three lead exposure groups which were matched with respect to social class. The high-lead exposure group had pre-natal blood lead values greater than 30 µg/dL whole blood; the intermediate group between 10 and 30 µg/dL; and the lowest group less than 10 µg/dL. A step-wise regression analysis showed that birth weight, a composite measure of home environment and socio-economic class of the father constituted the best set of predictors for Bayley MDI at 12 and 24 months. The possibility that birth weight might be a mediating variable between pre-natal lead exposure and sensorimotor deficit was explored by removing it from the regression model. Despite this change in the regression model, lead was not found to be a significant predictor of either 12- or 24-month MDI.

In addition to the Bayley Mental Development Scale, the Moore and Bushnell study administered the Bayley Infant Behaviour Record (IBR) to 12- and 24-month-old infants. The IBR assesses qualitative aspects of the infant's performance during the examination. The record consists of 30 items which rate the infant's social and objective orientations toward its environment as expressed in attitudes, interests, energy level, emotions and approach-withdrawal tendencies when stimulated. Correlations between IBR ratings and a composite index of lead exposure (maternal blood lead, home tap-water lead and pica at year 1 and 2) were all zero-order.

Although lead's effect on a large number of developmental outcome variables was assessed by Moore and Bushnell, no significant association between foetal lead exposure and sensorimotor development was found. However, these negative results do not provide unequivocal support for the null hypothesis. First, in these preliminary analyses the investigators apparently did not consider the possible interactions between foetal lead exposure and biological and social covariables. Like other obstetrical or perinatal insults, foetal or early post-natal lead exposure may most likely result in neurodevelopmental delay or deficit when it occurs in the context of initial biological risk (e.g. low birth weight) or social disadvantage (e.g. lack of early stimulation and/or physical neglect) (Pearson and Dietrich, 1985).

The purpose of the present prospective investigation was to extend the data base on the early behavioural effects of lead exposure with more frequent assessments of lead burden and behavioural development than previously attempted. In addition, we wanted to examine specifically the interaction between lead exposure and other potent developmental influences such as perinatal status and home environment.

Subjects

One hundred and two expectant mothers residing in pre-designated lead-hazardous areas of Cincinnati, Ohio, were recruited at the time of their first visit to a pre-natal clinic. The number of children available for this analysis represents about one-third of the subjects who will constitute the final sample at the end of this ongoing prospective study. The recruitment area was identified from the Cincinnati Lead Screening Registry as having a long history of including children with elevated blood lead levels. Results of other studies with these children have shown that lead from paint, dust and generally poor housing stock is the major contributor to body burden (Clark et al., 1985).

Forty-one per cent of the expectant mothers were recruited during the first trimester, 58% during the second and 1% in the third. Women who were drug-addicted, alcoholic, or diabetic, or those who had documented neurological disorders, psychoses or mental retardation, were excluded from recruitment. The mean age of mothers at delivery was 22.8 years (SD = 4.7). Ninety-six per cent of the mothers were single, and 89 percent were on public assistance.

Infants born at University Hospital were recruited at delivery. Infants of less than 36 weeks' gestation and/or 1500 g were excluded. In addition, infants must have had an Apgar score of greater than 5 at 5 m, and presented no serious medical condition such as Down's Syndrome, phenylketonuria, polycythemia or significant congenital anomaly.

Study infants had a mean birth weight of 3145 g (SD = 453 g), and mean gestational age by examination (Ballard et al., 1979) of 39.4 weeks (SD = 1.6 weeks). Eighty-three per cent of the infants were black, and 50% were female.

Methods

Assessment of Potential Confounders and Covariates

Undue lead exposure is known to covary with a number of social and biological risks which may mimic, obscure or otherwise interact with the effects of toxic exposure on neurobehavioural development (Milar et al., 1980; Hunt et al., 1982; Stark et al., 1982). Therefore, a significant amount of biological and social background data were collected on all subjects.

Obstetrical history and pertinent perinatal data were recorded from the neonate's and mother's charts. These data were then coded using the Littman-Parmelee Obstetrical and Postnatal Complications Scales (Littman and Parmelee, 1978).

The socio-economic status of the infant's family was assessed at 3 months post-partum with the Hollingshead 4-Factor Index of Social Status (Hollingshead, 1975). At 6 months, the quality of the infant's domestic environment was assessed with Caldwell and Bradley's Home Observation for Measurement of the Environment (HOME) (Caldwell and Bradley, 1985). The HOME combines interviewer's queries with direct observations to yield a total score which reflects the parent's responsivity and involvement with her infant, and the extent to which the physical environment and temporal routine are safe and stimulating. Each home visit was attended by two professionally trained observers who independently scored the HOME assessment. Interobserver reliability on the scale was 96% for this sample (sum of agreements divided by the total number of observations).

A total of eight potential covariates and/or confounders was chosen *a priori* based on their theoretical and/or expected empirical relationship with both the target-independent variable (lead exposure) and/or the target-dependent variable (behavioural development). These were: (i) obstetrical complications, (ii) post-natal complications, (iii) gestational age by examination, (iv) birth weight, (v) composite index of tobacco and alcohol use during pregnancy, (vi) home environment, (vii) socio-economic status, and (viii) race of infant (coded 1 = white, 2 = black).

These covariables were then tested for their confounding potential according to the recommendations of Dales and Ury (1978). Any variable associated with both blood lead and any index of behavioural development at a p value of 0.10 or lower was designated as a potential confounder. Furthermore, any variable associated with any index of behavioural development, but not blood lead, at a p value of 0.10 or lower was designated as a covariate. Variables meeting these criteria joined lead and behavioural development variables in the regression analyses. Of these eight covariables, post-natal complications (as measured by the Littman-Parmelee Scale), birth weight, socio-economic status and race were potential confounders. Gestational age qualified as the only covariate.

Assessment of Lead Exposure and Behavioural Development

Maternal blood samples were collected by venipuncture at pre-natal recruitment. Infant blood samples were collected at 10 days (corrected for gestational age), 3 months and 6 months post-partum. Blood was drawn by either heel stick, finger stick or venipuncture depending on the physical characteristics of the infant. The percentage of blood samples drawn by a method other than venipuncture was 42%, 24% and 29% at 10 days, 3 months and 6 months, respectively. Contamination of finger stick or heel stick samples has not proven to be a source of analytical error in our laboratory. In fact, at all ages, finger stick and heel stick samples have yielded slightly lower blood lead levels than venipuncture samples. This is exactly opposite to what one would predict if external lead contamination were a problem. All blood samples were analysed for lead by anodic stripping voltammetry using an extraction method (Morrell and Giridhar, 1976). All blood lead values were corrected for hematocrit and transformed to their natural logarithm. Quality control procedures for the analysis of blood are detailed by Bornschein et al. (1985).

Behavioural development was assessed at 3 and 6 months with the Mental Development Scale and IBR of the Bayley Scales of Infant Development. The Bayley Scales were administered in the morning at an inner-city health clinic by one of two professionally trained psychometricians. Care was taken to ensure that the infant was not noticeably ill, fatigued, hungry or under medication when examined. Intertester reliability was assessed at regular intervals throughout the study and averaged 0.96 (Pearson r) for the Bayley MDI. In addition, at least 85% agreement was maintained for each item of the Bayley IBR.

A principal axis factor analysis (SAS, 1982) of the IBR data set was executed to reduce the large number of rating variables to a few meaningful behavioural factors. Factor scoring coefficients were then used to calculate factor scores for individual subjects. The 3-month IBR factors were: (i) Attention/Motor Maturity, (ii) Positive Mood, (iii) Active/Energetic, and (iv) Sensory Interest. At about 6 months the IBR factors were: (i) Attention/Motor Maturity, (ii) Positive Mood, and (iii) Active/Energetic. Table 1 indicates the individual IBR variables involved in each factor at 3 and 6 months.

Data Analysis

Because of to the large number of independent and dependent variables in this study, a multi-variate multiple regression procedure (SAS, 1982) was used to reduce the probability of Type 1 error. These analyses included all independent variables (blood lead, confounders and all lead by confounder interactions) and dependent variables (either 3-month or 6-month MDI and IBR factors) at each age period. Because of the correlated nature of the blood lead variable, only one lead index was ever in any single multi-variate regression model. All interactions of blood lead with confounders were tested first. Non-significant ($p > 0.05$) interactions were dropped from the final models. The one covariate, gestational age, was included in the final models to increase the precision of parameter estimates (i.e. to increase the overall variance in behavioural development accounted for by the set of independent variables).

Results

Table 2 presents arithmetic means and standard deviations for pre-natal and post-natal blood lead levels during the first year. Post-natally, mean blood lead levels modestly increased from 5.1 µg/dL at 10 days to 7.7 µg/dL at 6 months. Interindividual variability in exposure was evident at all ages.

Table 1.

3- and 6-month Bayley Infant Behaviour Record factors.*

3-Month Assessment:

Attention/Motor Maturity

Object Orientation
Goal Direction
Attention Span
Social Orientation to Persons
Reactivity
Fine Motor Co-ordination
Mouthing of Toys
Gross Motor Co-ordination
Interest in Visual Stimuli
Interest in Manipulation of Objects

Active/Energetic

Activity
Interest in Body Movement
Energy Level
Gross Motor Co-ordination

Positive Mood

General Emotional Tone
Endurance
Social Orientation to Examiner
Fearfulness
Cooperativeness
Social Orientation to Mother

Sensory Interest

Interest in Visual Stimuli
Interest in Sounds
Interest in Vocalizing
Interest in Manipulation of Objects
Energy Level
General Emotional Tone
Interest in Banging/Throwing Toys

6-Month Assessment:

Attention/Motor Maturity

Attention Span
Goal Direction
Fine Motor Co-ordination
Reactivity
Object Orientation
Gross Motor Co-ordination
Interest in Manipulation of Objects
Interest in Banging/Throwing Toys
Energy Level
Interest in Visual Stimuli
Interest in Sounds

Positive Mood

General Emotional Tone
Endurance
Social Orientation to Examiner
Co-operativeness
Fearfulness (-)

Active/Energetic

Activity
Body Motion
Energy Level

* Variables are listed in ascending order by the magnitude of their factor loadings. All factor loadings are positive unless otherwise indicated.

Table 2.

Arithmetic means, standard deviations and low and high blood lead levels for each age.

Age	Mean Blood Pb (μg/dL)	Standard Deviation	Low	High
Pre-natal	8.2	3.6	1	21
10 days	5.1	2.9	1	15
3 months	6.0	3.7	1	18
6 months	7.7	5.4	1	36

Table 3 presents means and standard deviations for Bayley MDI at 3 and 6 months. Although some infants in the study scored poorly (e.g. MDI $\leq$ 80), the vast majority presented a normal to superior pattern of early sensorimotor development. In the US population, the Bayley MDI has an estimated standardized mean of 100 and standard deviation of 16. In this sample, the mean MDI at 3 and 6 months was 101 and 112, respectively. We attributed these higher mean developmental quotients to the large number of black infants in the study. Several investigations have shown that, as a population, African and American black infants display a faster rate of motor and sensorimotor development during the first year when compared with European and North American white infants (Scarr, 1983). As indicated later in this paper, these racial differences in developmental rate may play an important role in the differential vulnerability of infants to the early adverse neuro-behavioural effects of low-level lead intoxication.

After dropping the insignificant interactions of lead with confounding variables from the models, the test for the multi-variate linear hypothesis of an overall lead effect on developmental variables was significant only for the

Table 3.

Means, standard deviations and low and high high Bayley MDI scores for each age.

Age	Mean Bayley MDI	Standard Deviation	Low	High
3 months	101.5	10.1	71	125
6 months	112.0	16.1	78	150

lag relationship between 3-month blood lead and 6-month Bayley MDI and IBR factors (Wilks' Lambda = 0.8929, F (4,91) = 2.93, $p < 0.04$). In addition, there was a significant 3 month blood lead level by race interaction for Bayley MDI and IBR factors (Wilks' Lambda = 0.8687, F (4,91) = 3.44, $p < 0.02$).

To explore which dependent variables were affected by lead, a univariate multiple regression analysis (SAS, 1982) was executed including 3-month blood lead with all confounders, significant interactions and covariates. The results of this analysis are presented in Table 4.

Lead level at 3 months was significantly related to 6-month MDI and the IBR factors of Attention/Motor Maturity and Positive Mood. The 3-month blood lead level by race interaction was nearly statistically significant ($p = 0.06$) for MDI at 6 months and significant at conventional levels for the first two IBR fact- ors. To explore further the nature of the 3-month blood lead level by race inter-action, separate bivariate Pearson correlations were calculated for white and black infants. Table 5 presents the results of this analysis.

Clearly, the inverse relationship between blood lead level at 3 months and 6-month Bayley outcome measures was entirely contained in the small but

Table 4.

Univariate multiple regression results for 3-month blood lead and 6-month Bayley outcome variables.

Dependent Variable	Parameter	Estimate	Standard Error	t	p
MDI	PbB3*	-22.321	11.051	-2.02	0.04
	Post-natal complications	0.206	0.163	1.26	0.21
Model r^2 = 0.25	Birth weight	0.009	0.003	2.66	0.01
	Gestational age	2.050	0.925	2.22	0.02
	Race	-14.848	11.087	-0.09	0.92
	Social class	-0.030	0.322	-0.09	0.92
	PbB3 X race	11.000	5.960	1.85	0.06
Attention/Motor Maturity	PbB3	- 1.712	0.583	-2.93	0.004
	Post-natal complications	0.013	0.008	1.57	0.11
Model r^2 = 0.29	Birth weight	0.005	0.001	2.80	0.006
	Gestational age	0.093	0.048	1.92	0.05
	Race	- 1.374	0.585	-2.35	0.02
	Social class	- 0.006	0.017	-0.41	0.68
	PbB3 X race	1.010	0.314	3.21	0.001
Positive Mood	PbB3	- 1.356	0.640	-2.12	0.03
	Post-natal complications	0.008	0.009	0.92	0.36
Model r^2 = 0.15	Birth weight	0.000	0.000	0.25	0.80
	Gestational age	0.037	0.053	0.71	0.48
	Race	- 0.655	0.642	-1.02	0.64
	Social class	0.021	0.018	1.17	0.24
	PbB3 X race	0.737	0.345	2.14	0.03
Active/Energetic	PbB3	- 1.059	0.735	-1.44	0.15
	Post-natal complications	0.010	0.359	0.92	0.35
	Birth weight	0.0002	0.0002	0.83	0.40
	Gestational age	0.082	0.061	1.34	0.18
	Race	- 1.242	0.737	-1.68	0.09
	Social class	0.003	0.021	0.15	0.87
	PbB3 X race	0.698	0.396	1.76	0.08

* 3-month log blood Pb.

Table 5.

Pearson correlations between 3-month log blood lead and 6-month Bayley variables for black and white infants.

6-Month Bayley Scale Variables	White Infants (r) (N = 17)	Black Infants (r) (N = 85)
Mental Development Index	-0.52*	-0.05
Attention/Motor Maturity	-0.62**	0.18
Positive Mood	-0.50*	0.05

* p 0.05.
**p 0.01.

highly influential sample of white infants. As a further test of this finding, another multi-variate regression analysis was executed. However, in this analysis, race and the blood lead level by race interaction were excluded from the full model. In the original model, the parameter estimate for 3-month blood lead level on 6-month MDI was -22.32. This appeared to be a substantial main effect. For every log unit increase in blood lead level, there was an associated decrease of 22.32 MDI points. This 'effect' is equal to approximately 1.3 standard deviations on Bayley's original norms. However, such an interpretation of the main effect for 3-month blood lead level is unwarranted. In the presence of a strong statistical interaction (such as the blood lead level by race interaction), main effects are often uninterpretable (Kleinbaum and Kupper, 1978). Indeed, with racial factors absent from the model, the test of the multi-variate linear hypothesis of an overall 3-month lead effect on 6-month Bayley variables was non-significant (Wilks' Lambda = 0.9186, F

(4,93) = 2.06, p > 0.10). Further, in a univariate multiple regression analysis of the reduced model, the parameter estimate for 3-month blood lead level on 6-month MDI was reduced to a non-significant -2.76. Parameter estimates for 3-month log transformed blood lead on IBR factors were also non-significant in the reduced univariate multiple regression models.

As a further illustration, Figures 1, 2 and 3 plot 3-month log blood lead and infant performance on 6-month Bayley MDI and the first two 6-month IBR factors. The least-square regression slopes for black and white infants are also presented. The relationship between blood lead level and behavioural development was clearly zero-order for blacks. For whites, however, the relationship was negative, and does not appear to be unduly influenced by any single outlier.

Table 6 presents intercorrelations between blood lead assessments from the pre-natal period to 6 months. Interestingly, 3-month infant blood lead levels were most highly correlated with maternal or pre-natal blood lead. Further, 3-month blood lead level was equally correlated with 10-day and 6-month blood lead levels. For the most part, pre-natal and 10-day blood lead levels should represent early and late foetal exposures, respectively. The fact that both of these measures of foetal lead burden were correlated with 3-month blood lead levels suggests that the 3-month index of exposure essentially reflects pre-natal rather than post-natal intoxication. However, if foetal lead burden (as indexed by 3-month blood lead) is associated with poorer neurobehavioural development in white infants, the question arises as to why neither pre-natal nor 10-day blood lead level significantly predicted Bayley outcomes at 6 months in the multi-variate regression analyses.

FIGURE 1

PLOT OF BAYLEY MDI6 AND LN PBB BY RACE

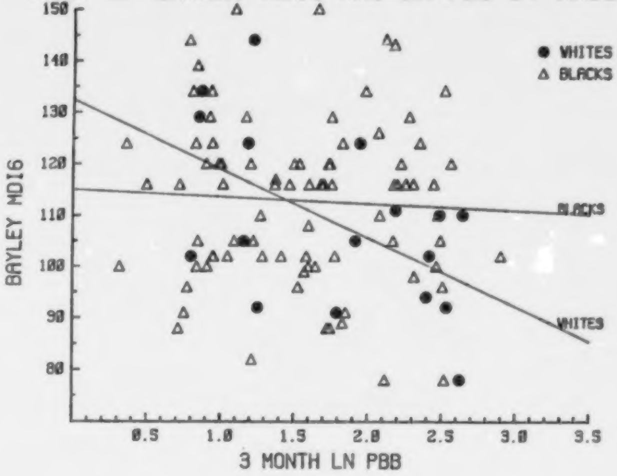


FIGURE 2

PLOT OF IBR FACTOR 1 AND LN PBB BY RACE

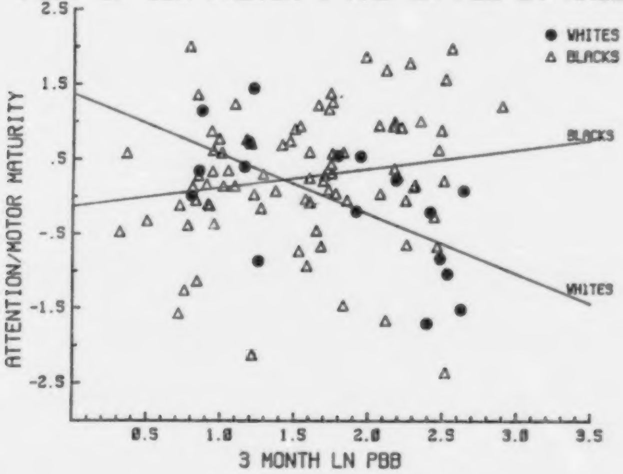
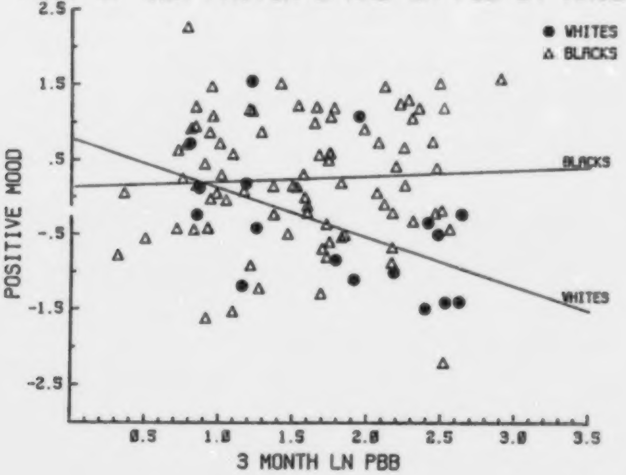


FIGURE 3

PLOT OF IBR FACTOR 2 AND LN PBB BY RACE



As 3-month blood lead levels appeared to be related to 6-month indices of behavioural development, the question naturally arises as to what kind of exposure 3-month blood lead level represents. The most significant issue is whether 3-month blood lead level represents mainly foetal exposure, post-natal exposure or some combination of the two.

Table 6.

Univariate multiple regression results for 10-day log blood lead level and 6-month Bayley outcome variables.

Dependent Variable	Parameter	Estimate	Standard Error	*t*	*p*
MDI	PbB10*	-30.636	13.798	-2.22	0.03
	Post-natal complications	0.195	0.167	1.17	0.24
Model $r^2 = 0.25$	Birth weight	0.010	0.003	2.87	0.005
	Gestational age	1.796	0.936	1.92	0.06
	Race	-21.026	12.422	-1.69	0.09
	PbB10 X race	15.454	7.236	2.14	0.03
Attention/Motor Maturity	PbB10	- 1.502	0.764	-1.96	0.05
	Post-natal complications	0.012	0.009	1.26	0.21
Model $r^2 = 0.23$	Birth weight	0.0006	0.0002	2.86	0.005
	Gestational age	0.087	0.052	1.69	0.09
	Race	- 0.968	0.688	-1.41	0.16
	Social class	-%2b%0.009	0.017	-0.52	0.60
	PbB10 X race	0.803	0.401	2.00	0.05

* 10-day log blood Pb.

To address these issues, two univariate multiple regression analyses were executed with pre-natal and 10-day blood lead levels in consecutive models. Pre-natal exposure, as indexed by maternal blood lead level, was not related to any index of behavioural development in this analysis. However, as Table 7 shows, although 10-day blood lead levels were not significantly associated with Bayley outcomes in the more rigorous and conservative multivariate regression analyses, in the standard univariate multiple regression analysis there was a significant main effect for 10-day blood lead level, and a significant 10-day blood lead level by race interaction on 6-month MDI and the IBR factor of Attention/Motor Maturity. Nevertheless, the main effect is still not interpretable in the presence of the strong blood lead level by race interaction.

Table 7.

Pearson correlations between 10-day log blood lead level and 6-month Bayley variables for black and white infants.

6 Month Bayley Scale Variables	White Infants (r) (N = 17)	Black Infants (r) (N = 85)
Mental Development Index	-0.56*	-0.08
Attention/Motor Maturity	-0.51*	0.02

* $p < 0.05$.

To determine the nature of the 10-day blood lead level by race interaction, separate bivariate Pearson correlations were calculated for white and black infants. As Table 8 shows, the 10-day blood lead 'effect' is wholly contained in the subsample of white infants. Figures 4 and 5 plot 10 day log

Table 8.

Correlation matrix for pre-natal and post-natal log blood lead (PbB).

	10-Day PbB	3-Month PbB	6-Month PbB
Pre-natal PbB	0.23*	0.42**	0.28*
10-day PbB	----	0.37**	0.05
3-Month PbB		----	0.37

* $p < 0.05$.
**$p < 0.01$.

blood lead level and infant performance on 6-month MDI and the IBR factor of Attention/Motor Maturity. The least-square regression slopes for black and white infants are also presented. As with 3-month blood lead levels, the relationship between 10-day log blood lead level and behavioural performance is clearly zero-order for blacks and negative for whites.

Taken together, results of the 10-day and 3-month blood lead analyses indicate that later foetal lead burden was associated with poorer neurobehavioural development as measured by the Bayley Scales of Infant Development at 6 months. However, this relationship held only for white infants. Black infants in this study were seemingly unaffected by either pre-natal or post natal low-level lead exposure.

In addition to being statistically significant, the effects of later foetal lead burden on the neurobehavioural development of white infants were substantial. In a final analysis, the adjusted parameter estimates for 10-day and 3-month log blood lead level on MDI at 6 months were calculated for white infants. With the exception of race, these parameter estimates were

FIGURE 4

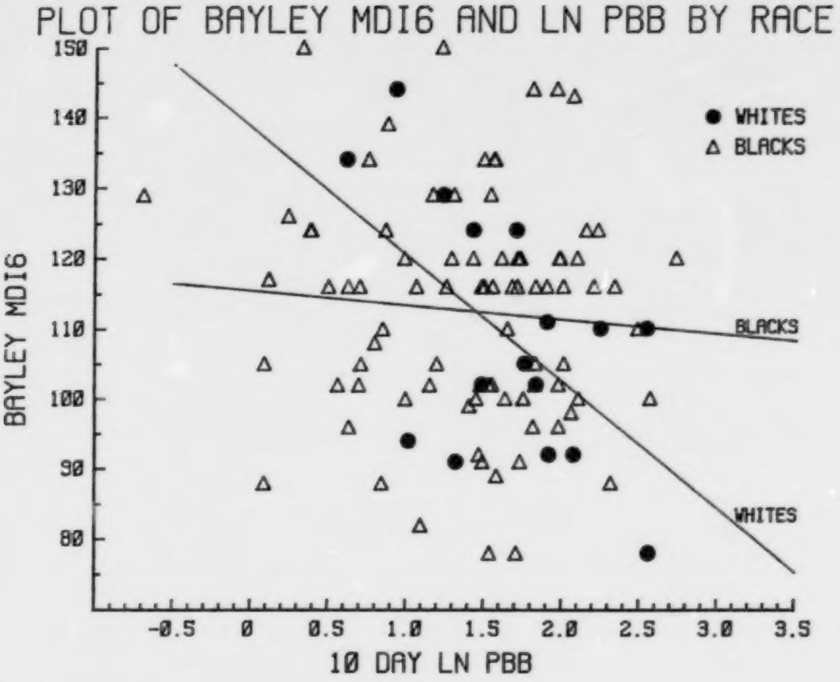
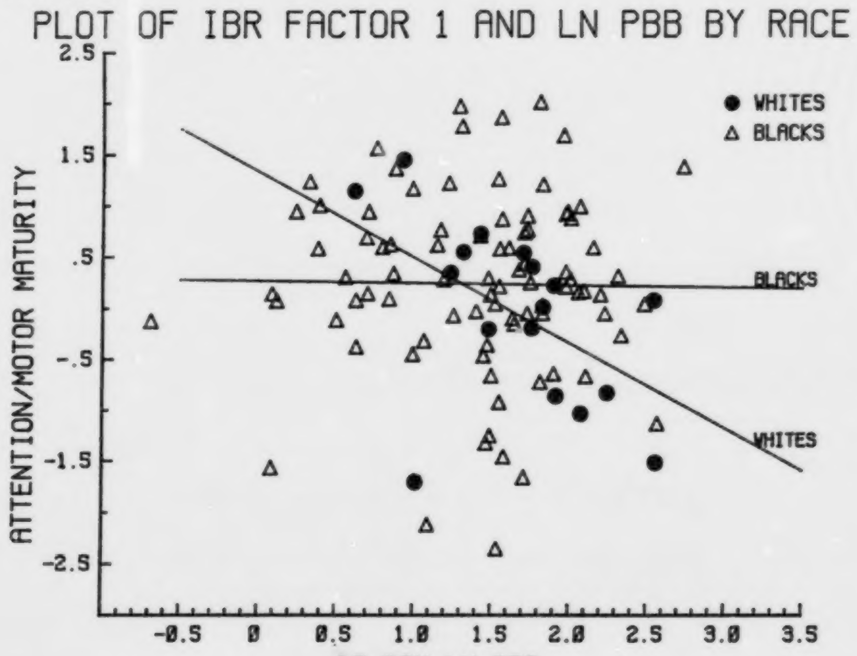


FIGURE 5



adjusted for all confounders and covariates in the original model. For white infants, a log unit increase in blood lead level at 10 days and 3 months was associated with a decrement of 16.2 and 6.9 MDI points, respectively. To summarize, later foetal lead exposure in white infants was associated with a decrease of one-half to a full standard deviation of 6-month Bayley MDI for each log unit of blood lead.

Discussion

A previous study of Bellinger et al. (1984) reported a small but statistically significant relationship between cord blood lead categories and Bayley MDI at 6 months; this was in a sample of low-risk, predominantly white infants. Post-natally, blood lead levels at 6 months were unrelated to 6-month Bayley MDI. In the present study, 10-day and 3-month blood lead levels in high-risk white infants were associated with substantial decrements in 6-month MDI.

Whereas results of the Bellinger et al. (1984) study and the present study are not directly comparable because of differences in blood sampling and characterization of exposure, they do converge upon the conclusion that foetal exposure to lead may result in small to substantial delays in the rate of early sensorimotor development. In the Bellinger et al. (1984) report, lead-related delays in sensorimotor development were extremely small. Perhaps this was due to the fact that the sample was already at low risk, and therefore buffered from the neurobehavioural effects of low-level intoxication. In contrast, the effects of later foetal lead exposure in the present investigation were substantial for white infants. This may have been due to the fact that they come from a high-risk population, and were therefore more vulnerable to the neurobehavioural effects of low doses of lead.

Race may be another important component of early vulnerability to the neurobehavioural effects of low-level foetal lead exposure. As mentioned earlier, black infants display a more rapid rate of sensorimotor development during the first year of life. This may imply that early neurological development in black infants is more canalized, and therefore resistant to minor forces which may perturb a normal course of early behavioural development (Waddington, 1957). Therefore, white infants may be more vulnerable to the early neurobehavioural effects of later foetal lead burden.

Although Bellinger et al. (1984) did not assess the interaction between lead exposure and race, it is nevertheless interesting that they reported small lead effects on behavioural development in a low-risk, predominantly white sample, whereas the present investigation found substantial lead effects on behaviour in a high-risk white subsample. One guarded conclusion from these two studies is that low-level foetal lead exposure is detrimental to early sensorimotor development, particularly among high-risk white infants.

Neither Bellinger et al. (1984) nor Moore and Bushnell (1984) reported a relationship between post-natal lead exposure and sensorimotor development. In the present study, no relationship was found between post-natal blood lead level at 6 months and concurrent neurobehavioural indices. However, none of these investigations can currently address whether pre-natal or post-natal lead exposure adversely affects higher cognitive funtions such as language and symbolic information processing. Such data await maturation of the longitudinal cohorts they are following.

Although the results of this interim study provide some support for the hypothesis that foetal lead exposure adversely affects early behavioural development, a final caveat is in order. This investigation's finding of an adverse neurobehavioural effect for lead is based on a relatively small subsample of study infants. These results, although compelling in light of the report by Bellinger et al. (1984), must be replicated within the Cincinnati Study with a full cohort of 6-month-old infants, and by the other longitudinal studies currently being planned or in progress (Bornschein and Rabinowitz, 1985). Nevertheless, the findings of this study and others suggest that pregnant women should avoid exposure to lead sources. Whereas 6-month MDI is a poor indicator of later neurobehavioural development, developmental delays in infants may lead to unsatisfactory caretaker-child interactions during the first year which may have lasting effects on development (Sameroff and Chandler, 1975).

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17. CHILDHOOD LEAD: IMPACT ON GROWTH AND DEVELOPMENT

A REVIEW OF EVIDENCE CONCERNING 'LOW DOSE' EFFECTS

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Lead poisoning has long been recognized as a potential cause of mortality or long-term morbidity in children (Byers and Lord, 1943; Chisolm and Barltrop, 1979). The developing central nervous system (CNS) is thought to be particularly susceptible to high-dose lead exposure (Lin-Fu, 1973), which can cause both acute and chronic neurological impairment.

During the past decade, controversy has arisen concerning the impact of low-dose ('subclinical') lead burden on the health, development and behaviour of children (Needleman et al., 1981; Colliver et al., 1983). No consensus exists about the contribution of lead to childhood performance. The issues are complex (Rutter, 1980), highly political (Marshall, 1983) and often supported by contradictory evidence.

Any discussion of the relationship between childhood function and body lead burden must be prefaced by consideration of the methodological problems inherent in this area of clinical investigation (Rutter, 1980; Trout, 1981; Medical Research Council, 1984). Measurements of body lead burden and of child performance are both complex, but are crucial to the study of any putative relationship between these variables. In addition, the structure of clinical studies undertaken to examine these relationships will determine the likelihood that the investigator is able to draw inferences from the data (Trout, 1981). These issues are reviewed briefly.

Blood lead has traditionally been used as the criterion for ascertainment of children's body lead burden. There is evidence, however, that blood lead level reflects only recent exposure and does not correlate well with cumulative body lead burden, duration of exposure or timing of exposure in the child's past (Chisolm and Barltrop, 1979). Depending upon one's view of the possible pathophysiology of lead poisoning, timing, peak dose, length of exposure or total body accumulation of lead (or some combination of these factors) may be the critical variable(s) (Ratcliffe, 1977). Unfortunately, only by frequent serial prospective measurement of blood lead from early life can one begin to determine the child's 'lead intake profile' (Bornschein et al., 1980).

More recently, investigators have begun to use tooth lead levels in children as an indicator of cumulative lead exposure (Needleman et al., 1979; Winneke et al., 1982; Smith et al., 1983). Even here, however, there are both technical and biological problems. Smith et al. (1983) found important differences in lead content between upper and lower central or lateral incisors of the same children, with variations of up to 30% more lead in upper incisors. In addition, they determined blood lead to tooth lead correlation coefficients up to 0.58, although most values ranged from 0.38 to 0.50. These observations show that the measurement of tooth lead can be quite variable within the same child, and that there is at best only a relatively modest correlation between tooth lead and blood lead values.

Deciding what aspects of child performance to measure poses additional problems. Whereas some early investigators used standard IQ measures, more recent studies have attempted to assess additional aspects of children's functions thought to influence the performance components of standard tests. Thus, observations of visual and auditory processing, attention and memory, and studies of reaction time have been undertaken. Teachers' judgements of classroom behaviour and social function have also been added to standardized testing.

Several problems arise when one considers the dilemmas posed by measurement of children's behaviour and intellectual function. Firstly, one must use standardized measures of known reliability and validity. In many areas of childhood behavioural and neuropsychological function, such measures are not available. Secondly, if one is seeking evidence of subtle dysfunction in children with increased lead burden, one requires measures of considerable sensitivity. However, where the differences between groups are small, but real, based on the capacity of measures to detect minor alterations of function, one is left to ponder the clinical significance of these small distinctions between groups. Thirdly, the more tests one does, and the larger the sample size is, the more likely one is to detect statistical differences by chance (Type I error).

A major methodological difficulty in lead-behaviour research concerns the type of studies undertaken to assess relationships of lead to performance (Anonymous, 1978). In the absence of any possibility of human experimental study of the lead-development question, investigators must resort to descriptive analyses of groups of children with varying degrees of body lead burden. The lead burden may be ascertained early in life, and the child followed forward in time to measure developmental and behavioural outcomes, usually in comparison with a control group (cohort or prospective analytical survey) (Trout, 1981). Attempts are made to match subjects with the abnormality of interest (increased body lead) to controls with similar socio-demographic characteristics who differ with respect to body lead levels. The underlying assumption is that the factors on which the groups are matched are the potential confounding variables. However, matching is often difficult, with resulting uncertainty about the validity of findings.

Cross-sectional analytical surveys assess simultaneously the exposure and outcome of the population under study. Relatively little time passes between measurements of exposure and outcome, so that the rate of development of abnormality (incidence) cannot be adequately assessed. Cross-sectional studies can at best yield evidence of correlation between variables, but can never speak the actual truth or direction of the association. Thus, for example, the finding of impaired development in children with increased body lead could be interpreted as a noxious effect of lead on development (Needleman et al., 1979), or as a developmental factor pre-disposing to increased lead ingestion (Graham, 1979), or as evidence of the covariance of social and developmental factors determined by impaired parenting (Milar et al., 1980).

Studies Reporting Lead Effects on Behaviour and/or Development

The best-known and most widely quoted recent study purporting to establish links between body lead burden and neuropsychological and behavioural performance in children is the paper by Needleman et al. (1979). Several further reports of the same data set, sometimes with additional data, have appeared as extensions of the original 1979 report (Burchfiel et al., 1980; Needleman, 1981, 1982, 1983; Bellinger and Needleman, 1983).

Over 3300 Grades 1 and 2 children in two communities near Boston constituted the study population. Deciduous teeth for lead analysis were contributed by 2146 children (70%), and their teachers rated almost all of them on an 11-item forced choice classroom behavioural scale. The results were reported to demonstrate a dose-response relationship between increasing dentine lead and poorer performance in several of the categories of behaviour (e.g. distractibility, lack of persistence).

Subsets of students representing the lowest and highest deciles of tooth lead were recruited for detailed neuropsychological study. A total of 524 children was provisionally eligible (258 with low lead, 187 with high lead and 79 'unclassified'). Of these, 158 children (100 high lead and 58 low lead) were ultimately studied and reported. An effort was made to control for potential confounders (factors which might influence the outcome of interest and also be associated with the independent variable) such as parental attitudes to child-rearing, parental IQ, social class and past medical history.

A summary of the findings includes the following observations: high-lead children were reported to perform less well on WISC-R (a widely used standardized assessment of children's intelligence), on several measures of auditory and visual processing, on attentional performance as assessed by reaction time under varying conditions, and on most items of teacher-rated behavioural function. Although several subsequent papers have appeared reporting on aspects of the 1979 study (Burchfiel et al., 1980; Needleman, 1981, 1982, 1983; Bellinger and Needleman, 1983), the major critique of Needleman's work focusses on the methodology and analysis of the primary report. If these criticisms are accurate, one must review all the subsequent reports in the context of these comments.

Two expert committees, one in the US and the other in Great Britain, have reviewed Needleman et al.'s (1979) work very carefully. The American group was convened early in 1983 by the United States Environmental Protection

Agency "to provide independent peer review of selected studies" concerning the health effects associated with lead exposure (EPA, 1983). The group comprised nationally recognized experts in educational psychology, child development and biostatistics. The British Medical Research Council (1984) group was similarly constituted, and carried out a review substantially like that of the EPA-sponsored committee.

Both panels of reviewers were highly critical of many aspects of the Needleman et al. (1979) work. There was considerable concern about the accuracy and validity of indicators of lead exposure, including criticism of both technical and strategic aspects of the work. With regard to psychometric evaluations of children, concerns were expressed about the validity of the WISC-R assessment as undertaken in this study. Errors were noted in calculations of parental IQ. Low-lead children were tested early in the study, in an apparently non-random fashion. As well, the teacher questionnaire was an instrument of unknown reliability and validity, the value and properties of which were uncertain.

At the methodological level, criticism was expressed about the low rate (30%) of reporting of the original 524 eligible subjects. The analyses undertaken were criticized on grounds of arbitrariness of classification of some data, missing data points and selective reporting of significant results with exclusion of non-significant, but possibly relevant, observations. The EPA-sponsored committee concluded that "the study results, as reported in the Needleman et al. (1979) paper, neither support nor refute the hypothesis that low to moderate levels of lead exposure lead to cognitive or other behavioral impairments in children" (EPA, 1983).

Needleman responded to the criticism of the panel, correcting some errors and reanalysing his data in accordance with the statistical procedures suggested (Needleman, 1983; Needleman et al., 1985). The results substantially confirmed those presented in his 1979 paper that a decrement of about 4 IQ points is associated with dentine lead levels that appear to correspond to blood lead levels in the 30-50 µg/dL range. Some epidemiological problems relating to possible confounders are, however, as yet unresolved, and the relationship of dentine lead to blood lead levels has not been satisfactorily defined.

Other studies report positive associations between increased body lead and neurodevelopmental function. The study of Winneke et al. (1982) assessed the association of neuropsychological performance and tooth lead in 115 German children. This group was selected from a cohort of 311 volunteers drawn from a total potential population of 3669 children living near a lead smelter. No significant association was found between tooth lead and verbal or full-scale IQ, after controlling for confounders. Nonetheless, there was a non-statistically significant inverse correlation between verbal IQ and tooth lead levels. There was also a statistically significant association between tooth lead level and performance on the perceptual-motor integration test, as well as some evidence of significant associations of lead and 3 of 11 behavioural dimensions assessed. In all cases, however, the proportions of variance explained by tooth lead were small.

One pilot study by Yule et al. (1981) showed a statistically significant inverse relationship between blood lead levels and IQ in 166 of 195 children aged 6-12 years living near a lead works in London, England. However, the authors themselves cautioned that these data were preliminary and required careful interpretation, as there had been inadequate control and measurement of important confounding socio-demographic variables. In a subsequent larger study, Yule and Lansdown (1983) tested 194 of 221 children, using the same measures as those in the pilot study. In this investigation, extensive evaluation of relevant socio-cultural factors was undertaken. After controlling for confounding variables, no association was demonstrated between full-scale IQ, or tests of educational attainment, and blood lead levels.

Studies Reporting Absence of 'Lead Effects'

Several studies have appeared which fail to detect associations of lead with behavioural or psychometric function. The best executed of this group is the study of Smith et al. (1983). Four hundred and three of 432 eligible children were evaluated on a battery of tests of general intelligence, educational attainment, visual attention and memory, verbal and auditory attentional performance, neurological assessment and motor co-ordination. Mothers were interviewed at length and were tested for intelligence. Parents and teachers both contributed ratings of child behaviour.

Analysis of the results was done taking account of the several variables shown to influence child IQ (maternal IQ, parental interest, family characteristics, marital relationships, and sex of child). Controlling for these factors, IQ measures were found not to differ significantly across lead groups. For some subgroup analyses of subtests of performance, small statistically significant differences by lead group were detected, the importance of which remains unclear.

Harvey et al. (1984) reported findings similar to those of Smith et al. (1983) in 131 (of 188) 2-year-old Birmingham children. They detected no statistically significant associations between body lead and intelligence or behavioural measures. McBride et al. (1982) studied 400 pre-school children in Sydney, Australia, with blood lead levels ranging from 2 to 29 µg/dL. Measures of verbal intelligence, motor activity and a parental rating of child behaviour were completed. No significant relationships were found between blood lead and these aspects of performance. Yule and Lansdown (1983) summarized results of four surveys carried out in Britain involving approximately 1000 children, reported during the early 1980's. They concluded that:

> taken together [these studies] suggest that low levels of lead exposure may account for a small (less than 5%) proportion of the variance of children's intelligence. The effect is stronger in children from less privileged social backgrounds. Because of the confounding effects of social factors, it is difficult to conclude that the relationship between lead and intelligence is a causal relationship.

Interim observations from three prospective longitudinal studies of the effects of lead on child development were presented to the Commission in March 1985 by Dietrich (p. 269). These data are rather conflicting. The Boston study (Bellinger et ai., 1984) reported an inverse and statistically significant relationship between three levels of cord blood lead (but not 6-month concurrent logarithmic values of blood lead) and 6-month mental development scores. In a subsequent paper, Bellinger et al. (1985) reported the strength of this association to be attenuated during the second year. The association was found only at cord blood lead levels between 10 and 25 µg/dL. Children with post-natal blood lead levels above 10 µg/dL did not show similar mental development deficits. The Glasgow data (Moore et al., 1982), on the other hand, failed to find any significant relationships between measures of maternal blood lead burden and Bayley mental, psychomotor or behavioural indices at 12 or 24 months.

The Cincinnati study's interim results suggested an overall effect of 3-month blood lead on 6-month Bayley scores (Dietrich et al., 1985). These findings were, however, complicated by an interaction between blood lead level at 3 months and race. When this relationship was explored further, it was found that a small subsample of white infants showed a strong inverse relationship between blood lead and Bayley scores, whereas the majority of (black) infants did not show any statistically significant relationships between lead and development. These observations were interpreted as possibly showing a differential vulnerability of certain groups of infants to the neurobehavioural effects of lead, although the authors cautioned that more data are needed to substantiate all of these reported findings.

In his summary, Dietrich argued that post-natal lead exposure between 6 and 24 months post-partum does not appear to be related to delays in early behavioural development. On the other hand, pre-natal exposure to lead may have minor to substantial effects on neurobehavioural development, depending on the exposed population. What is clear, however, is that further follow-up and study of these populations are required before clear and definitive conclusions can be drawn.

Yule and Rutter (1985) undertook an extensive review and reanalysis of a number of neuropsychological investigations of children published since 1979 in an effort to discern whether there is a consistent pattern of results across studies. Children in these studies had blood lead levels ranging from 0.5 to 35.5 µg/dL; dentine or whole tooth lead concentrations ranged from 1.4 to 38.5 ppm. Following detailed consideration of technical and methodological aspects of this body of research, the authors concluded that "the neuropsychological effects of lead within the range seen today in ordinary environments without special high risks are quite small". This conclusion takes account of both statistically significant and statistically nonsignificant studies. The authors judged that lead accounts for not more than 2-3% of the variance of cognitive performance in children. This is equivalent to the 2- to 5-IQ-points difference often observed between low- and high-lead groups in the studies referred to. In population terms, however, a 5-point shift in IQ means a doubling of children with IQ less than 70 (Rutter, 1980; Needleman, 1983). All these studies with positive findings report differences in the same direction.

Electrophysiological Studies

A few recent studies have explored the relationship between body lead and electrophysiological functions in children (Burchfiel et al., 1980; Guerit et al., 1981; Otto et al., 1981, 1982; Otto, 1986). Burchfiel et al. (1980) examined electroencephalograms (EEG's) of 41 children (22 low-lead and 19 high-lead) selected from the cohort of 158 children reported on by Needleman et al. (1979). A few (6%) of 320 features of the EEG data were found to differ significantly ($p < 0.05$) between children with high and low tooth lead. As pointed out by a peer review critique (Medical Research Council, 1984), however, this proportion is close to the 5% of significant results expected by chance at p less than 0.05 if no association exists between body lead and EEG.

These investigators then selected the single feature of the EEG which most strongly differentiated the low-lead and high-lead groups, and combined this factor with other psychological data in a discriminant analysis to compare high- and low-lead groups. Group separation was found to be highly significant. However, this technique of post hoc selection of significant data for inclusion in subsequent analysis is an unacceptable statistical procedure, as the same data are used for both hypothesis generation and hypothesis testing.

Two studies by Otto et al. (1981, 1982) reported an association between serum lead levels and slow wave cortical potentials elicited by EEG. The first study presented data on 63 of 100 children who participated in the study. The others were rejected for reasons of young age, non-compliance or technical, medical or behavioural problems. No information was given to indicate whether the excluded subjects differed systematically from those reported. Using a complex statistical analysis of particular slow wave components of the EEG function, the authors reported an interaction with blood lead and age. That is, slow wave voltage decreased with increased blood lead in younger children, but tended to vary directly with blood lead in children over the age of 5.

The later study (Otto et al., 1982) was a replication of the previous work on a subsample of 28 of the same children 2 years later. Here slow wave potentials showed correlations with both contemporaneously drawn blood lead and the blood lead levels measured 2 years earlier. These results were interpreted as showing not only that lead produces altered central nervous system function, but that the effects persist over time. Once again, however, the nature and selection of the clinical sample were unknown, and the numbers small.

In a recent review of his own and other work, Otto (1986) summarized what appear to be relevant findings from current clinical neuropsychological studies. He pointed to the conflicting results of the studies referred to above (Otto et al., 1981, 1982) attempting to relate serum lead in children to slow wave EEG voltages elicited in an active conditioning test. He referred to inconsistencies in studies of the effects of lead exposure on visual evoked potential in both humans and animals.

However, very recent work by Otto and colleagues (1985) found that, for lead exposure above 25 µg/dL, "brain stem auditory evoked potentials increased directly with the maximal blood lead values found in the child's medical records." The significant increase in hearing thresholds with increasing lead exposure history suggests that lead impairs hearing and the peripheral segment of the auditory pathway. Although these findings are tantalizing as explanations of the putative learning problems of lead-exposed children, Otto pointed out that further comprehensive studies of audiometric and electrophysiological functions of children and adults are required to resolve these issues.

The study by Guerit et al. (1981) evaluated 79 children, divided into three subgroups, living within 2.5 km of a lead smelter in Belgium. A neurophysiological battery was created consisting of EEG (including frequency analysis), visual evoked potentials, brain stem auditory evoked potentials and eye movement analysis. The subgroups showed variable correlations between serum lead level and electrophysiological scores, one group having a negative correlation of 0.40 ($p < 0.05$) and a second (and apparently more seriously) affected group showing a positive correlation of 0.26. No differences in prevalence of neurophysiological abnormalities were found when the total population was divided into distinct blood lead or free erythrocyte protoporphyrin classes.

In summarizing the state of the art with respect to studies such as these using electrophysiological measurements, the MRC Review Committee commented as follows (Medical Research Council, 1984):

> the health implications of EEG measurements are poorly understood and difficult to interpret. Most if not all of the many measurements that can be obtained from recording electrical brain activity have at present no known meaning in terms of psychological functioning. Even if some

measurements differ between low and high lead groups, it is impossible to say whether the differences indicate a harmful or a beneficial effect.

Congenital Malformations

Needleman et al. (1984) published a study relating pre-natal lead exposure and minor congenital anomalies. Cord blood was collected from 5183 neonates (97% of the total) delivered in one Boston hospital over a 1-year period. Approximately 75% of the mothers were interviewed to collect demographic information and medical, reproductive and drug histories. A subsequent chart review of the infants' records was undertaken to reveal and classify malformations. The records had been compiled by house officers blind to the cord blood levels.

Analysis was done to define maternal and neonatal variables associated with increased cord blood levels. Logistic regression analysis was then done, controlling for confounding variables, to evaluate the contribution of lead to the risk of malformation. Results suggested that minor but not major malformations were associated with increased cord blood levels.

Several problems in the execution of this study are worth noting. Firstly, in this retrospective study no evidence is given of the accuracy of the medical records which were audited. Nor is any interrater reliability between chart abstracters presented. Secondly, the results of the relationship between cord blood lead level and minor anomalies are presented and discussed at length. However, no account is taken of the curious (and statistically significant) inverse relationship between cord blood lead level and respiratory distress. Thirdly, there is apparently no specific pattern of malformations associated with lead levels. In view of the well-known teratogenic effects of, for example, thalidomide, rubella, alcohol and phenytoin, each of which produces a characteristic spectrum of clinical malformations in the newborn, it seems odd that there is an apparent non-specific effect of lead on the foetus.

Finally, in the statistical analysis of the observations, a "variety of logistic regression analyses" was undertaken in an effort to produce statistical models to account for the findings. However, the more analyses that are done, the greater the likelihood of finding statistically significant results. In these circumstances it is often appropriate to divide one's p values by the number of analyses done. There is no evidence that this procedure was followed in this study.

Growth

One recently published report (Schwartz et al., 1986) analysed the association between childhood blood lead level and stature. Using data from the second National Health and Nutrition Examination Survey (NHANES II), the authors produced linear regression models of adjusted data from 2695 children aged 7 and below. They demonstrated that the models used to account for height, weight and chest circumference were all more significant when serum lead level was included than when the regressions were run without lead. It is difficult to judge the relative contributions of lead to growth, in relation to the other significant variables such as age, race, sex and hematocrit. The authors argued that at the mean age of this population (59 months), the mean blood lead level of the child "appears to be associated with a reduction of 1.5% in the height that would be expected if their blood lead level had been zero." It is difficult to understand how this judgement is made.

In summarizing these observations, the authors commented that blood lead level may be a surrogate for a multiplicity of environmental factors. Other investigators have produced evidence suggestive of a correlation between aspects of the caretaking environment and childhood lead levels (Milar et al., 1980; Hunt et al., 1982; Stark et al., 1982). It is therefore plausible that the apparent association between serum lead level and linear growth reflects a host of social-emotional, nutritional and/or cultural variables. The direct biological effects of lead on growth remain to be established in carefully executed longitudinal surveys.

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18. EFFECTS OF LEAD ON NERVE CONDUCTION

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Introduction

There is still much controversy as to what constitutes a "safe level" of exposure to lead. In regard to the peripheral nervous system, a classical sign of peripheral neuropathy due to lead poisoning is weakness or paralysis of the muscles that are most commonly used (e.g. wrist drop). Lead poisoning occurs at levels between 80 and 100 µg/dL (and over) in adults. Because of uncertainty as to peripheral nerve functioning in the absence of clinical disease in individuals with lower blood lead levels, this question continues to be investigated mainly on adults exposed to lead in the workplace, although a few studies do exist on children. Earlier studies on lead and nerve conduction investigated lead workers with blood lead levels 80 µg/dL and over (Catton et al., 1970; Seppalainen and Hernberg, 1972). Later studies sought to clarify the effects of lower lead exposure on nerve conduction studies in workers with blood lead levels of 70 µg/dL and below.

In reviewing the existing literature, we have put emphasis on human studies.

Pathological Nerve Changes

Animal Studies

A recent extensive review of the effects of lead exposure on the physiology of neurons was published by Audesirk (1985), describing the effects on neuronal structure (morphology), physiology (function) and subcellular mechanism. For our purposes the more pertinent aspects of Audesirk's review are axonal morphology and myelination, as well as the effects on the conduction velocity, as studied on animals.

Experimental studies chronically exposing adult rodents for several months to inorganic lead generally demonstrated segmental demyelination of individual axons. The demyelination results from direct injury to Schwann cells. Nevertheless, proliferation of Schwann cells also occurs, and there seems to be an ongoing process of demyelination and remyelination.

In vitro studies show that rapidly myelinating cell cultures (derived from mouse dorsal route ganglions) exposed to lead for long periods experience demyelination with the axons remaining intact.

Relatively few studies on nerve conduction in lead-exposed animals relate their findings to morphological nerve changes. Fullerton (1966) tested lead-poisoned guinea pigs. He found the conduction velocity of the posterior tibial nerve to be reduced in less than half of the animals, and segmental demyelination occurred in all those showing marked reduction of conduction velocity. Hopkins (1970) chronically poisoned baboons with lead and observed them over 1 year. Although he induced severe symptoms of lead poisoning, he did not find statistically significant changes in nerve conduction velocities, and observed only minimal histological evidence of peripheral nerve damage without segmental demyelination. Purser et al. (1983) used cynomolgous monkeys and injected them with doses of lead acetate for 9 months, achieving blood lead concentrations of 90-100 µg/dL. Maximal motor nerve conduction velocity (MNCV) was insignificantly decreased. The conduction velocity of slow fibres, however, was significantly increased. Histological examination of the nerves revealed some 'minor' nerve fibre degeneration with associated myelin degeneration, but no evidence of segmental demyelination. Purser et al. concluded that "the discovery of nerve fibre degeneration, when there was no effect on the MNCV .... showed that histological changes can exist in the presence of apparently normal physiology".

Human Studies

Histological nerve studies in lead-exposed humans are rare. They were done mainly in cases of lead poisoning with clinical evidence of lead neuropathy and, in those instances showed evidence of axonal degeneration (Herter, 1895; Laslett and Warrington, 1898; Simpson et al., 1964; Behse et al., 1972). Buchthal and Behse (1979) undertook a nerve conduction study on 20 lead-exposed men with maximal blood lead levels in the preceding year ranging from 70 to 140 µg/dL. They also biopsied the sural nerves of eight of them and of two men with peripheral neuropathy, one of whom was suspected to have lead neuropathy. Histologically, these workers found no evidence of segmental demyelination in the patient with lead neuropathy nor in the eight lead-exposed men. There was a marked loss of large fibres in the patient with lead neuropathy, characterized by loss of axonal nerve fibres. In the eight lead-exposed men, the slowing of the conduction velocity of the sural nerves was not found to be associated with loss of large myelinated fibres (axonal loss). Teasing of fibres of the nerves of the eight men showed minor abnormalities. Some teased fibres had several large internodes with an inappropriately small diameter. The authors stated that "it is not certain whether the thin internodes are a sign of onset of primary demyelination or of axonal damage". No dose-response relationship was found between the incidences of electrophysiological or histological abnormalities and the maximal or average blood lead levels. The authors concluded that the small reduction in conduction might be due to a slight change in the properties of the nodal membrane. They did not consider the slowing in nerve conduction to be a sign of subclinical neuropathy.

In summary, the morphological nerve studies of lead-exposed animals such as rats and guinea pigs appear to show mainly segmental demyelination. Histological nerve studies of lead-exposed primates and lead-intoxicated symptomatic humans revealed mainly axonal nerve damage. However, Buchtal and Behse's histological examination on lead-exposed men who had no clinical evidence of neuropathy but who had slowed nerve conduction found neither segmental demyelination nor axonal degeneration but only signs of changes in the axonal membranes.

It is still not clear what kind of histopathological nerve changes are present in asymptomatic, lead-exposed individuals with slowed nerve conduction. Only further histological studies could shed more light on this question.

Nerve Conduction Studies in Humans

As already mentioned, the effects of lead on nerve conduction have been studied mainly in the occupational field on symptomatic lead-exposed workers. A few studies exist on children.

Physiological Considerations of Nerve Conduction

Conduction studies on peripheral nerves measure the motor and sensory responses of the nerve to an electrically applied stimulus. The more frequently tested peripheral nerves in the literature are the medianus, ulnaris, peroneal, posterior tibialis and suralis nerves. Different measures of conduction have been described for both sensory and motor nerves in the literature, the most common and more consistently used being nerve conduction velocity, latency and action potential amplitude.

Defining Nerve Conduction Parameters

Maximal Nerve Conduction Velocity (MNCV). The maximal motor conduction velocity (MMCV) measures the performance of the fastest (larger diameter) motor nerve fibres. The nerve is stimulated by two electrodes placed at different distances from the recording electrode and the time differences (i.e. the differences in the latency periods) in the muscle response to the two stimulating electrodes are measured. To calculate the sensory conduction velocity (SCV), the distance between the stimulating and recording electrodes is divided by the sensory latency period. The conduction velocity of slow motor fibres (CVSF) is a further, more refined technique.

Latency Period. The latency period is the time that elapses between the electric stimulation of the nerve and the onset of an electric response. In the case of motor nerves (Distal Motor Latency Period (DMLP)), the latency period includes the period of nerve conduction, of transmission at the neuromuscular junction, and of the response of the muscle. In the case of sensory nerves (Sensory Action Potential latency (SAP latency)), the latency measures directly the time needed for the nerve conduction, and no other structures are involved.

Action Potential Amplitude. Neural stimulation of muscle fibres leads to a compound action potential composed of all fibres of a motor unit (Motor Action Potential amplitude (MAP amplitude)). It can be easily recorded from skin electrodes. The sensory action potential is recorded solely from the nerve fibres, as no amplification is coming from many fibres as in the muscle (SAP amplitude). Sensory potentials are small. Computer averaging techniques are used to measure them.

Pathophysiology of Nerve Conduction (Raminsky, 1985)

Nerve conduction velocity depends on fibre diameter and on the degree of myelination. In unmyelinated nerve fibres, an impulse is propagated continuously along the fibre. Conduction velocity increases with increasing fibre size. In myelinated axons, there is in addition saltatory or 'jumping' conduction at the levels of the nodes of Ranvier. Conduction velocity increases with increasing myelination.

Nerve lesions can affect the axon or the myelin sheath or both. Demyelination of the nerve fibres results in a substantial reduction of nerve conduction.

Neuropathies that affect primarily the axons usually produce an axonal degeneration that starts distally and proceeds proximally (Wallerian type of degeneration). The process is called a dying-back reaction. In experimentally induced axonal neuropathy, fibres with the largest diameter, which also conduct the fastest, have been consistently shown to be more susceptible to intoxication and degenerate earlier. The remaining thinner fibres are still capable of conducting an impulse, although more slowly. Axonal degeneration alone results in only slightly increased latency periods and reduced nerve conduction velocity. Depending on the extent of the lesion, the latency or nerve conduction velocity may still be within normal range. Often only comparison of an affected group of individuals with a normal group may reveal a reduction in the mean of nerve conduction measurements.

Synopsis of the Literature on Nerve Conduction

Adults

A study by Catton et al. (1970) is one of the earliest nerve conduction studies carried out in relation to lead exposure. Of the 19 lead-exposed male study subjects employed in the manufacture of lead acid accumulators, 5 showed symptoms of excessive lead absorption. The exposed men were compared with 17 male hospital workers of similar age distribution. The blood lead concentration in the control group was not determined. Seven workmen had blood lead levels above 120 µg/dL, 6 above 80 and 6 above 40 µg/dL. Conduction studies of the lateral popliteal nerve were carried out. There was considerable variation of the individual measurements. Neither motor nor sensory maximal velocity was significantly different. However, the motor potential amplitude stimulated at the knee and expressed as a percentage of that stimulated at the ankle was significantly different between exposed and non-exposed groups.

Seppalainen and Hernberg (1972) tested 39 lead workers and 39 age-matched controls. Of the 39 exposed workers, 31 had a previous diagnosis of lead poisoning, but there was no clinical diagnosis of neurological disease. Lead levels in whole blood, δ-aminolaevulinic acid (ALA) and hemoglobin were measured. Workers were subdivided into categories according to their symptoms related to clinical poisoning and to their blood lead levels (40-80 and >80 µg/dL). The motor conduction velocity (MCV) of median, ulnaris and lateral popliteal nerves and CVSF of the ulnar nerve were determined. The means of nerve conduction tests for the exposed workers were compared with those of their controls. The conduction velocities were significantly lower in the exposed cases, although marked abnormalities were not present. The mean ulnar CVSF showed the greatest changes.

Seppalainen et al. (1975) reported on another project in which the study subjects were 28 workers (male and female) of a storage battery factory, whose blood lead levels had been regularly monitored for the previous 4-5 years.

Their current blood lead concentrations ranged between 28 and 65 µg/dL, never having exceeded 70 µg/dL. The blood lead values of the controls were estimated to be 10-13 µg/dL. Motor and sensory conduction velocities from the median, ulnar, deep peroneal and posterior tibialis nerves as well as ulnar CVSF were measured. A comparison between exposed workers and controls showed significantly decreased means for motor conduction velocities of the median and ulnar nerves and for the CVSF of the ulnar nerve. Electromyograms on 11 workers with abnormal or borderline velocities showed nine abnormal results, compatible with peripheral neurogenic lesions.

Araki and Honma (1976) tested 36 male lead-exposed workers from different work sites and compared them with age-matched healthy controls. There was no further information characterizing the controls. The blood lead determinations of the exposed workers were current ones which ranged from 2 to 73 µg/dL. Information on past exposure was not given. Other biological indicators of internal lead absorption were measured ALA dehydratase (ALAD) and the lead mobilization test following EDTA administration). The conduction velocities of the median and tibial posterior nerves were correlated with blood lead, ALAD and lead mobilization. The distal median MCV and the distal median mixed nerve conduction velocity showed consistently significant correlations for the three lead absorption parameters. The MCV of the posterior tibial nerve correlated only with blood lead levels. The correlation analysis included only the exposed workers and there was no control for age, so that a possible positive bias cannot be excluded. When the means of the nerve conduction velocities were compared between lead workers with blood lead concentrations of 25-73 µg/dL and controls, the reductions of the mean velocities for lead workers were statistically significant.

A small study that may indicate that nerve conduction may not be directly related to contemporary levels of lead is the one conducted by Feldman et al. (1977) on a group of steel bridge demolition workers exposed to lead oxide fumes. Two groups were selected for studies of conduction velocity on the peroneal nerve: 13 burner workers (mean blood lead level 79.5 μg/dL) and 6 non-burner workers (mean 48.8 μg/dL). The mean MCV was 43.2 m/s for burners and 49.0 m/s for non-burners. When the two groups were combined (mean = 45 m/s), the difference from the control men who had MCV of 54.1 m/s became statistically significant.

Lilis et al. (1977) studied 158 workers from two secondary smelters whose duration of lead exposure varied from less than 1 to more than 10 years. A third of the workers examined had blood lead levels below 60 μg/dL (range 30-60) and 29% were above 80 μg/dL (maximum 110). Of the 24 control workers, none had blood lead levels above 60 μg/dL. In 158 of the workers, nerve conduction velocity (NCV) of the radial and peroneal nerves was measured. No correlations were found between nerve conduction velocity and blood lead or zinc protoporphyrin (ZPP) levels. A finding described as having "potential importance" was that a significant decrease in nerve conduction velocity could occur in young workers in the early period of their work experience.

The effect of lead at subtoxic (< 80 μg/dL) levels on the behavioural and neurological functions was studied by Repko et al. (1978) in a group of 85 battery workers with a mean blood lead level of 46.0 μg/dL. The average blood lead level of any worker in the preceding 5 years had not exceeded 80 μg/dL. Fifty five controls (mean blood lead level 18.0 μg/dL) were selected from employees of the same plant, taking care to obtain a sample that had a comparable average for age, sex, height and weight. The control group, however, had a larger proportion of college graduates; the mean difference in the average level of education was 1 year. The measurements taken were the median MCV, the ulnar MCV, SCV and CVSF and the tibial and peroneal MCV's. Not all conduction velocities could be determined in all cases. Motor and sensory velocities, with the exception of the ulnar CVSF, were found to be slower in the experimental group, the differences being statistically significant. Correlation coefficients between nerve conduction velocity and blood lead levels were paradoxically of a positive sign; the correlations were very low, only the ulnar MCV coefficient reaching statistical significance (see also Ehle, 1985). The authors did not offer an explanation for this finding, which was similar to the results obtained by Ashby (1980).

In a study by Buchtal and Behse (1979), 20 lead-exposed men from a lead smelter and refining factory were selected because of blood lead levels of 70-140 µg/dL within the previous year. Seven of the men presented discrete neurological abnormalities, but these were not considered evidence of neuropathy; two other men had signs of clinical neuropathy. The following tests were conducted: determination of blood lead concentration, neurological examination, electromyography, nerve conduction studies and nerve biopsies. The nerve conduction parameters of the controls were 'expected' values estimated for age on large population series. The authors found that the differences in the means of some of the tested nerve conduction parameters when comparing exposed workers with controls were significant but relatively minor (within normal values). Paradoxically, they found significant increases in the sensory amplitudes of the median and peroneal nerves. The cause of the increase of amplitude is not clear. The electromyographic findings showed few and unimportant abnormalities. There were no characteristic findings of peripheral neuropathy. The findings of the histological examination of the biopsied sural nerves are reported above.

Seppalainen et al. (1979) studied nerve conduction in 78 lead-exposed workers from different work areas. Thirty-four unexposed workers served as controls. They had similar sex distribution, education and work activities. The reference group was younger than the lead-exposed group. The lead-exposed workers were grouped by their maximal blood lead concentrations. The difference between the mean age of the reference group and the mean ages of the lead-exposed groups ranged from 1.6 years for the lowest exposure group (maximal blood lead level (PbB max) 40-49 µg/dL) to 7.9 years for the highest exposure (PbB max > 70 µg/dL). The blood lead levels of the lead-exposed workers had been monitored regularly since 1969. The current blood lead level of all exposed workers averaged 34.3 µg/dL; for the controls it was 10.5 µg/dL.

As measures of the current and past blood lead concentrations, the current (at the time of examination), the maximal (maximal blood lead levels ever measured) and the time-weighted average values were used.

Comparisons of nerve conduction measurements between lead workers with maximal blood lead concentrations under 70 µg/dL and controls showed significant changes of nerve conduction parameters; many of these significant changes were present in subgroups with maximal blood lead levels of 40-45 and 50-59 µg/dL. The authors also did regression analyses as well as an analysis of the proportion of abnormal nerve conduction tests, although age corrections were not made. The correlation coefficients were significant for 4 of the 12 parameters tested.

Paulev et al. (1979) examined neurophysiological lead effects in 32 asymptomatic lead workers from a lead and zinc mine. The maximum period of exposure was 3 years. The 14 controls were office workers of the same mine and students with similar age distributions. Blood lead concentration in the lead workers was 53 ± 16 µg/dL, never having exceeded 80 µg/dL; in the controls it was 11 ± 4 µg/dL. The left and right ulnar MCV's were tested. No significant differences in nerve conduction tests were found between the groups. The small number of participants, particularly of controls, may have posed a problem for detecting any meaningful differences. Also, only the MCV of the ulnaris nerve was used, a nerve that has not been shown to be particularly sensitive to lead.

Ninety-four exposed male battery factory workers from different work sites were age-matched with 94 controls in a study by Ashby (1980). The controls included manual and office workers. The mean blood lead level of the exposed workers was 60 ± 15 µg/dL. The exposed workers had no symptoms or history of peripheral neuropathy. Past exposure was not further identified. The blood lead concentrations of the controls were not mentioned. Besides blood lead, a series of other tests was conducted (free erythrocyte protoporphyrin (FEP), hemoglobin, ALAD, ALA). Ulnar, median, radial and peroneal nerve conduction tests were performed. Means in lead workers were compared with those of the controls and found to be significantly reduced in the exposed workers. Among the correlation analyses between nine lead absorption indicators and nerve conduction variables, they found only one significant correlation between ulnar MMCV and blood lead level. As to the relationship between length of exposure and nerve conduction, the MMCV's for the ulnar and the median nerves were statistically significant in the multiple regression analyses. A paired analysis between lead exposure and matched control gave a statistically significant result for four of the five nerve conduction measurements among workers exposed for less than 2 years; in this group of workers, blood lead levels tested every 3 months were never found to be higher than 80 µg/dL.

Baloh and Spivey and co-workers conducted a longitudinal prospective study of 69 lead smelter workers and 35 control workers in an aluminum processing facility (Baloh et al., 1979; Spivey et al., 1980). Baseline and follow-up studies were 12-18 months apart. On follow-up, the authors were faced with various problems related to loss of follow-up and exclusions of exposed workers, to a change of the examining neurologist and laboratory technician and to a probable systematic laboratory change in measuring blood lead level.

Initially, the exposed workers had a mean blood lead concentration of 61.3 ± 12.8 (SD) µg/dL, and the concentration of the controls was 22 ± 5.9 µg/dL. Follow-up blood lead measurements were approximately 20% higher. The examinations included measurements of lead absorption (i.e. whole blood lead, ALAD, FEP, hematocrit), a standard neurological examination, nerve conduction measurements, electro-oculography and audiometric testing.

In the baseline testing, none of the motor (ulnar, peroneal) and sensory (ulnar, sural) nerve conduction variables differed significantly between the exposed and the control groups. In the lead group there was a significant negative correlation between blood lead concentration and MCV and CVSF of the ulnar nerve.

The results in the follow-up study revealed a significant decrease of the ulnar MCV among the exposed workers. Blood lead level and ulnar MCV remained significantly (negatively) correlated.

Johnson and Burg (1980) reported on a nerve conduction study as a component of a larger cross-sectional medical survey on 403 workers from primary non-ferrous smelters. MCV values were obtained for the ulnar and peroneal nerves for male and female employees and 305 controls. Male workers were subdivided into lead smelter workers (mean blood lead levels 56.1 µg/dL) and zinc plant workers (39.3 µg/dL); the controls' mean blood lead level was 15.2 µg/dL. Female workers were subdivided into smelter workers (mean blood lead level 29.5 µg/dL) and clerical workers (15.8 µg/dL), the controls having a mean of 10.3 µg/dL. The results obtained are somewhat contradictory. All groups had values within the normal range but all exposed groups had decreased MCV compared with the controls. The difference was statistically significant, however, only for the peroneal MCV in female smelter workers and in male zinc workers. These results are obviously inconsistent with the blood lead levels of the groups. The authors commented that their failure to find a substantial decrease in smelter workers could be due to the lower blood lead levels in their study subjects. The results also draw attention to the possible competing or interactive effects from other heavy metals.

In an attempt to clarify the uncertainties as to the level of blood lead at which electrophysiological changes become detectable, Bordo et al. (1982) studied 62 lead-exposed smelter workers, all of whom had mean blood lead levels below 50 µg/dL in the previous 2 years and had less than 10 years of exposure to lead. Twenty-seven hospital maintenance workers with similar mean age and age range were chosen as controls. Measurements of exposure were the maximum and average blood lead levels over the 2 years prior to the study period, the current levels and the length of exposure in years. Neurophysiological measurements of the median, peroneal and sural nerves were taken. Statistical tests of significance with analysis of covariance (age as covariate) were applied. Differences in the means of motor and sensory conduction variables were significant when lead workers were compared with controls as well as when lead workers were stratified by maximal blood lead levels (i.e. PbB max < 50 µg/dL; 50-69 µg/dL; > 70 µg/dL) in the 2 years prior to the study period. The authors pointed out that nerve conduction impairments were present in workers with the lowest blood lead levels, but were more severe in workers whose blood lead levels had exceeded 70 µg/dL at least once in the last 2 years. They also indicated that the electrophysiological abnormalities they found were more evident in workers with shorter (<2 years) exposure.

Seppalainen and Hernberg (1982) conducted a prospective study on previously unexposed male and female workers who were newly employed in a storage battery plant. Of 89 new employees, 23 stayed for a year and could be reevaluated, and a further 15 workers remained for the 2-year follow-up. The workers were matched by age, sex and initial conduction velocity with unexposed controls who were manual workers from a cable and power plant. The mean blood lead concentration of the controls was close to 10 µg/dL. The mean blood lead level of the exposed workers increased from an initial blood lead mean of 15.6 ± 6.2 µg/dL (measured after 6 weeks of employment) to 30.6 ± 9.1 µg/dL after a year, and remained constant thereafter. The mean of the maximal blood lead concentrations after 1 year was 36.9 ± 10.2 µg/dL. The nerve conduction results after 1 and 2 years were similar. Of the 15 parameters measured, the motor distal latency as well as the distal sensory conduction velocity of the medianus nerve were found to differ significantly from the controls. The conclusion of the authors was that nerve conduction impairment was more marked among those workers whose blood lead levels had quickly risen above 30 µg/dL, the maximal blood lead level within the groups being 48 µg/dL. The exact meaning of the term maximal blood lead level as used in the article is unclear, however, given that the group mean (PbB max) of the 2-year group was 36 ± 13.1 (SD) µg/dL, indicating that at least some of the blood lead measurements were above 48 µg/dL.

Ninety-one neurologically asymptomatic employees of a lead-smelting plant and 22 non-exposed controls sampled randomly from a population health study were tested for their blood lead concentration and underwent nerve conduction studies (Nielsen et al., 1982). The blood lead levels of the lead workers had been monitored for the previous 5 years, and workers with blood lead levels exceeding 70 µg/dL were temporarily removed from exposure. The mean blood lead level of the exposed workers was 51.0, with a maximum value of 91 µg/dL; that of the controls was 10.0. The MCV, distal latency and amplitude ratios of median, radial and peroneal nerves were determined. There was no significant difference in the means between the two groups.

Lead-exposed workers of a storage battery plant (Rosen et al., 1983) were selected on the basis of their blood lead values of the previous 2 years. They were divided into three groups: Group L--low exposure, mean blood lead levels <25 µg/dL, no individuals above 30 µg/dL, n = 16; Group M--medium exposure, n = 8; Group H--high exposure, blood lead level >40 µg/dL, n = 15. Median age and age range as well as the range of length of exposure were similar in the three groups. Surveillance at the workplace with regular blood lead measurements had existed for approximately 10 years prior to the study. Workers with blood lead levels over 70 µg/dL were routinely removed from exposure until levels were lowered to 40 µg/dL.

The neurophysiological tests of the study included nerve conduction studies, electromyogram and psychophysical thresholds (vibrometry, temperature, sensitivity). Covariance analysis was used for determining statistical differences of the means of the three groups. The means of the neurophysiological parameters were age-adjusted. The means of some motor and sensory nerve conduction parameters of the median and sural nerves were significantly different when the three exposure groups were compared. None of the electromyographic or psychophysical parameters showed significant differences between the three groups.

Singer et al. (1983) conducted a study on 40 automotive workers, 22 of whom were exposed to lead at work at all times, and 18 only intermittently. Thirty one controls were selected from a different site as being not exposed to lead by history, but for whom blood lead measurements were not available. Age- and temperature-adjusted values indicated a statistically significant decrease in conduction velocity for the median sensory and the sural nerve in the subgroup employed for less than 10 years, compared with the controls. The subgroup employed for over 10 years additionally had a significantly lower conduction velocity for the median motor nerve. The prevalence of nerve conduction abnormalities (i.e. a conduction velocity slower than 99% of the population at the subject age) was found to increase for sensory nerves from 20% at lead levels below 40 µg/dL to 25% at levels between 40-70 µg/dL and to 45% at levels above 80 µg/dL of blood lead. Motor nerves were not similarly affected. Correlation coefficients for the four NCV measurements, after standardization, were run for blood lead and zinc protoporphyrin levels. This was done for workers exposed to lead for less or more than 10 years. Only the correlation with sural nerve velocity was statistically significant, and only in workers exposed for less than 10 years.

Sborgia et al. (1983) conducted a comprehensive neurophysiological evaluation on 31 workers of a storage battery plant, using 37 workers of a small iron foundry as controls. The tests performed included neurological ones (tendon reflexes and muscular strength), nerve conduction studies and visual evoked potentials. Mean blood lead levels were 62.5 µg/dL for the lead workers and 23.6 µg/dL for the controls. All exposed workers received 1 mg EDTA daily for 3 days. Of 14 nerve conduction measurements, only 1 (lateral popliteal nerve amplitude) showed a significant difference between cases and controls (8.4 ± 8.8 (SD) versus 10.5 ± 4.1); none of the nerve conduction measurements correlated significantly with current, maximal and time-weighted average blood lead or zinc protoporphyrin levels (except one paradoxically positive correlation with ulnar motor velocity and ZPP).

The study was set up to develop a battery of measurements intended for ongoing monitoring of lead-exposed workers, and the authors' conclusion was that no single test, except perhaps the visual evoked potential response, was useful for the purpose.

Niney-nine lead-exposed factory workers and 61 unexposed assembly plant workers underwent a neurological examination, neurobehavioural testing and blood and urine analyses for lead absorption (Baker et al., 1984). Blood lead concentrations of exposed and unexposed workers overlapped considerably. Both groups were therefore combined and stratified into four groups according to their current blood lead levels: < 20 µg/dL, N = 26; 21-40 µg/dL, n = 97; 41-60 µg/dL, n = 28, and 61-80 µg/dL, n = 9. One hundred and seventeen subjects had nerve conduction tests on the ulnar, peroneal and sural nerves. Motor conduction in the ulnar and peroneal nerves did not deteriorate with increasing blood lead concentration except for reductions in the amplitude of the evoked motor potentials in the ulnar nerve. Modest slowing of sensory conduction and reduction of response amplitude were seen in the sural nerve. Regression analysis confirmed these associations. In most instances, current and cumulative exposure indices correlated equally well with outcome variables. Baker et al. (1984) concluded that their failure to confirm impaired motor nerve conduction velocity was probably due to the relatively low lead exposure (no cases above 80 µg/dL) in their series, and that such dysfunctions require at least 6 months of continued exposure at levels above 60 µg/dL.

Triebig et al. (1984) examined nerve conduction in lead-exposed workers from a storage battery manufacturing plant. One hundred and thirty-three out of 148 men were eligible. Two exposed workers were matched by age and alcoholic intake to one control. The controls had various backgrounds (students, white- and blue-collar workers). Several biological indicators of lead were determined (PbB, FEP, ALAD, ALA). Blood lead values measured were the current level, the maximal level in the previous 5 years and the time-weighted average (TWA). When the lead-exposed group was compared with the controls, there was a mild but significant reduction in sensory nerve conduction velocity of the distal ulnar and medial nerves. In the multiple stepwise regression analyses, significant correlations were found between TWA-blood lead levels and motor and sensory nerve conduction velocities of the median and ulnar nerves. The lead-exposed workers were grouped into five categories according to their TWA-blood lead level. No slowing of nerve conduction velocities compared with age-matched controls became apparent in the groups with blood lead levels below 70 µg/dL. A significant effect was found only in the group with a blood lead level over 70 µg/dL.

Blood lead tests and neurophysiological tests were performed on 46 workers exposed to lead in a company that manufactured lead-based stabilizers (Jeyaratnam et al., 1985). Unexposed workers from a previous study served as controls. The mean blood lead level of unexposed Singapore workers was 15.8 ± 2.7 µg/dL, and that of exposed workers was 48.7 ± 40.4 µg/dL. There was no further information on the previous lead exposure of the study subjects or on the control group. The following tests were performed: blood lead concentration, nerve conduction studies, scalp somato-sensory evoked potentials and EEG (for 20 workers). With regard to the nerve conduction tests, there were slight but significant differences for the distal latency and MCV of the median and posterior or tibial nerves.

Lead Exposure and Nerve Conduction Tests in Children

Feldman et al. (1973, 1977) and Landrigan and Baker (1976) reported on nerve conduction studies in lead-exposed children. Feldman and co-workers studied 24 Boston and 33 Baltimore children who in their past had evidence of elevated blood lead (>40 µg/dL), other evidence of lead intoxication over 60 µg/L, urinary output following EDTA administration or radio-opaque flecks in the intestinal tract. A scattergram indicated that most children were between 1 and 12 years of age; there were, however, eight subjects aged 13-28 in the Baltimore group. Twenty-two children from non-risk areas between 19 months and 10 years of age were selected as controls.

The peroneal MCV was determined on all subjects. The means of the MCV's were lowest in the Boston group (the area with highest pollution), followed by the Baltimore group, and highest in the controls. All differences were significant.

Landrigan and Baker (1976) studied the prevalence of lead absorption in children living near a primary smelter. Five- to 9-year-old children with blood lead levels of 40 µg/dL or more were matched by age and sex to children with blood lead levels below 40 µg/dL. None of the 202 children had any clinical evidence of neurological abnormalities. The authors tested the peroneal MCV. No overt pathologic measurements were found. A correlation analysis revealed a significant negative correlation between blood lead level and MCV, providing, according to the authors, modest evidence for an association between lead intake and subclinical motor neuropathy.

Feldman et al. (1977) studied 26 children with long-term exposure to lead paint. Their blood lead levels, as well as peroneal MCV, were determined. Ten children had a motor conduction velocity that was one standard deviation below the control mean (unexposed children of the 1973 study by Feldman et al.). Those children were considered to have increased body lead burden and were recommended for chelation, regardless of their blood lead values. The mean blood lead level of the 10 children was 32.6 µg/dL, not significantly higher than that of the other children with normal MCV (27.8 µg/dL). Consent for chelation was obtained from the parents of the seven children. A possible relationship was found between slowing of MCV and the quantity of lead excreted in the urine after chelation.

Each of the three studies presents major methodological problems. Feldman et al. (1973) compared inner-city children and older individuals with children from non-risk areas. However, blood lead levels and exposure times were very loosely determined, and the age ranges were wide and not controlled.

Doubts were cast that an appropriate matching was done in Landrigan and Baker's study. Re-evaluations with matching of the data for confounders before comparing mean values (Gartside and Panke, 1977; Ehle, 1985) did not reveal statistically different means.

Feldman et al.'s (1977) study group had no controls. The sample size of the children being chelated was too small to draw conclusions regarding dose-response relationships.

Discussion of Nerve Conduction Results

Some Problems in Making Comparisons

A comparison of the nerve conduction studies is complicated because of differences and problems in the methodologies. In particular, the following issues should be considered:

1) Exposure histories. Blood lead indicates only the current exposure to external lead. Most lead workers were exposed to lead over many years. The degree to which the current lead exposure or the long-term cumulative exposure affects nerve conduction is not known. It is thus important to know the exposure histories--the length and degree of past exposure--otherwise associations attributed to current blood lead levels may in reality be attributable to much higher blood lead levels in the past. To at least in part account for past lead exposure, some authors analysed the maximal blood lead levels ever recorded, the average blood lead levels over a given time period or time-weighted average blood lead levels in addition to current blood lead levels.

2) Quality control of blood lead measures. Blood lead determinations were done in different laboratories. It is important that strict laboratory quality controls concerning accuracy and precision were in place.

3) Measuring nerve conduction. The various researchers used slightly different methods of measuring nerve conduction (i.e. different equipment and methods of stimulating and recording nerve conductions). A constant skin temperature over 30°C seems to be an important factor for the accuracy of the measurements. To eliminate variability or bias within a study, a standardized

approach to measuring nerve conduction is necessary. The examiner should also be blind with respect to the blood lead levels of the individuals tested.

4) Confounding factors. The following factors influence nerve conduction studies and should therefore be eliminated, by stating exclusion criteria, by matching or by adequate statistical analysis:

- age--negative correlations with NCV or amplitude; positive correlation with latencies
- alcohol abuse, leading to alcoholic neuropathy with changes in nerve conduction
- occupational exposure to neurotoxic substances
- medical conditions, leading to peripheral neurology (i.e. neurological diseases, chronic renal insufficiency, metabolic diseases, especially diabetes mellitus).

5) Choice of controls. Ideally, controls should be comparable with the exposed groups in their work characteristics, except for the exposure to lead. Manual workers may not be comparable with office workers, as the former are more likely to have traumatized nerves of exposed sites (e.g. the ulnaris nerve at the elbow). Controls should have no exposure to suspected or known neurogenic substances. Usually the work characteristics of the controls are not well described and it is difficult to judge the adequacy of the controls.

6) Statistical analysis. Multiple comparisons in univariate analysis increase the probability of finding a significant result by chance. Multiple comparisons can be identified in many nerve conduction studies. In most instances, however, this problem is mitigated because of highly significant results or consistency in results.

Table 1 provides a comparison of the methodologies used by the various

Table 1.

Methodological aspects of nerve conduction tests in relation to blood lead levels in adults studied.

AUTHOR (YEAR)	QUALITY CONTROL BLOOD LEAD	STANDARDIZATION OF NSV TESTS	TEMPERATURE CONTROL	BLINDING OF EXAMINER	EXCLUSION CRITERIA	CONTROL FOR AGE	WORK CHARACTERISTICS OF CONTROLS
Catton '70	?	?	+	?	±	+	Hospital Workers
Seppalainen '72	?	+	+	?	+	+	Students & Manual Workers
Seppalainen '75	+	?	+	?	+	+	Manual Workers
Araki '76	+	+	?	?	+	+	Manual Workers
Feldman '77	?	?	?	?	?	?	Manual Workers
Lilis '77	Y	+	?	?	-	-	Manual Workers
Repko '78	?	+	+	?	-	+	Other Employees of Same Plant
Buchtal '79	+	?	+	?	+	+	General Population Estimates
Paulev '79	+	?	?	?	+	+	Students & Office Workers
Baloh '79	?	+	?	+	?	+	Manual Workers
Seppalainen '79	Y	+	+	?	+	-	Manual Workers
Ashby '80	?	+	+	+	+	+	Manual & Office Workers
Spivey '80	?	+	?	+	?	+	Manual Workers
Johnson '80	+	+	+	+	+	+	Workers (Zinc Plant)
Bardo '82	?	?	+	?	+	+	Hospital Workers
Seppalainen '82	+	+	+	?	±		Manual Workers
Nielsen '82	?	+	+	?	?	±	General Population
Singer '83	?	+	+	?	+	+	Manual & Lab Workers
Rosen '83	+	+	+	?	+	+	Not Applic.
Sborgia '83	?	+	+	+	±	+	Manual Workers
Baker '84	+	+	+	?	+	±	Manual Workers
Triebig '84	+	+	+	+	+	+	Students, Manual & Office Workers
Jeyaratnam '85	+	?	+	?	±	-	Manual Workers

authors.

The characteristics of the studies are compared in Table 2. Most studies were cross-sectional, i.e. the blood lead level determinations were performed at the same time as the nerve conduction studies. Two studies (Spivey et al., 1980; Seppalainen and Hernberg, 1982) were follow-up studies.

The mean ages of the exposed workers ranged from 26.8 to 41 years. Individual ages ranged from 17 to 63 years. The mean blood lead concentrations ranged from 29 to 66.2 µg/dL. This does not include the studies by Catton et al. (1970) and Buchthal and Behse (1979) in which very high blood lead levels can be assumed. The range of the exposure period was wide, usually ranging from a few months to a maximum of 46 years.

Differences Between Nerve Conduction Measurements

All the articles reviewed tested for significant differences of the means between exposed workers and controls, or made comparisons with workers with lower exposure levels. The range of blood lead levels in the exposed workers was usually wide (Table 2) and differed from one study to the next.

Nerve conduction tests were also performed somewhat differently in each study. These differences make it difficult to determine whether any specific nerve conduction test would give significant results more consistently than the others. In his analysis of 19 studies, Ehle (1985) concluded that statistically significant differences in nerve conduction velocities were found more frequently (53%) for all the sensory nerves studied than for the motor nerves. Median nerve sensory differences were the most frequent (83%), followed by the sural (50%) and the ulnar nerves (29%).

It is not surprising that in our review of 23 studies we reached qualitatively similar results, as the majority of the studies were considered

Table 2.

Comparison of Exposure Characteristics of Reviewed Studies.

Authors	No. of Exposed	Blood Lead Levels µg/dL (Rounded)		Length of Exposure		Comments
		$\overline{x}$ ± SD	Range	$\overline{x}$ ± SD	Range in Years	
Catton '70	39	-	40-124	-	5/12-13	
Seppalainen '72	39	?	?	-	2.5/12-22	No known PbB in controls 40-80 and 80+ in exposed
Seppalainen '75	26	40 ± 9	28-65	4.6	1-17	
Araki '76	36	29 -	2-73	18	1-46	
Feldman '77	13	79 -	44-100	-	4/12-1	
Lilis '77	134	-	30-110	-	<1-10	
Repko '78	85	46 ± 14	? -79	8.7 ± 6.9	3/12-34	
Buchtal '79	20	-	70-140	-	4/12-33	Range of PbB max Previous Year
Paulev '79	32	53 ± 16	-	-	2/12-37	
Seppalainen '79	78	34 ± 10	-	8.4	-	
Baloh '79	69	61 ± 13	-	11 ± 9.2	-	
Ashby '80	94	60 ± 15	-	-	6/12-33	
Spivey '80	69	61 ± 13	-	11 ± 9.2	-	
M Pb Johnson Zn '80 F Zn+Pb	164 194 45	56 ± 13 39 ± 17 30 ± 14	-	12.4	-	
Bordo '82	62	42 ± 12	-	4 ± 2.7	5/12-10	
Seppalainen '82	23	31 ± 9	-	-	0-2	Results of Follow-up at First Year
Nielsen '82	91	51 ± 16	-	>9		
Singer '83	37 13	60 -	28-94	-	<10 >10	
Rosen '83	39	-	<25-70	-	6/12-28	Average PbB Over Previous Years in 3 Classes
Sborgia '83	31	62 ± 19	23-62	7.8 ± 3.1	-	Given EDTA 1 mg x 3 days
Baker '84	117	33 -	10-80	-	-	
Triebig '84	133	53 -	22-90	11	-	
Jeyeratnam '85	46	49 ± 14	? -90	-	-	

in both reviews. We found that, combining all measurements (velocity, amplitude and latency), differences occurred more frequently (57%) for the median nerve (both motor and sensory), followed by the peroneal (42%) and CVSF (37%). Sensory changes overall were more frequent (52%) than motor changes (38%). We are, however, not confident that the differences we found indicate any particular conduction measurement or specific nerve tested is likely to give more consistent results (Table 3).

Relationships Between Nerve Conduction Findings and Exposure

Despite the somewhat erratic pattern of the nerve impairments discussed in the various studies, there is little doubt that high levels of blood lead (i.e. > 70 μg/dL) can impair nerve conduction (Feldman and Hayes, 1977; Singer et al., 1983; Triebig et al., 1984). Such impairments are 'clinically significant' beyond the expected individual variations at toxic lead levels, but at lower values the impairments found are, in most cases, within 'normal ranges'. As well, there is less consistency between reports as to whether impairments are found at levels below 70 μg/dL, and more particularly in the range 30-40 μg/dL, a level shared by the majority of individuals occupationally exposed to lead.

Few studies have presented data classifying the cases into different ranges of blood lead levels which might allow identification of a threshold below which no measurable effects have been observed. Seppalainen et al. (1979) and Bordo et al. (1982), for example, found effects already present at levels below 70 μg/dL, whereas Triebig et al. (1984) and Singer et al. (1983) did not. Seppalainen et al. (1979) subdivided the study subjects in 10 μg/dL ranges from <40 to >70. One out of the 12 parameters measured was found significant at the 40-49 μg/dL range. This was, however, an unusual observation

Table 3.

Significant differences of the mean of nerve conduction measurements between cases and controls.

Authors	MEDIAN						ULNAR						PERONEAL						POST TIBIAL	POPLITEAL						SURALIS			CVSF		
	MOT			SENS			MOT			SENS			MOT			SENS				MOT			SENS			SENS					
	[1] V	A	L	V	A	L	V	A	L	V	A	L	V	A	L	V	A	L	V	V	A	L	V	A	L	V	A	L	M	U	P
Catton '70																				0	0		0	0							
Seppalainen '72	+	+					+													+										+	
Seppalainen '75	+			0			+			0			0						0											+	
Araki '76	+				+												+		+												
Feldman '77													+																		
Lilis '77													0																		
Repko '78	+						+			+			+																0		
Buchtal '79	+	0	+	+[2]									0	0	+	+	+									+	0				
Paulev '79							0		0			0	0		0													0			
Seppalainen '79	0		+				0			0			0						+							0				+	
Baloh '79							0																								
Ashby '80	+						+			0			+	+															0	0	0[3]
Spivey '80							+		0			0	0		0													0			
M Pb							0						+																		
Johnson Zn																															
'80 F Zn+Pb							+						+																		
Bordo '82	+	0	0	+	+	0							0	0	+												0	0			
Seppalainen '82	0		+	+			0			0			0						0							0	0			0	
Nielsen '82[5]	0		0										0		0																
Singer '83				+									0																		
Rosen '83	0		0	0	+		0		0				+						0							+	+				
Sborgia '83	0	0	0				0	0	0																						
Baker '84							0	+	0	0	0		0	0	0				0	0	0	0				+	0				
Triebig '84				+			0			+																					
Jeyeratnam '85				0			+							+												0					
Proportion of Significant Results	11/22			9/13			8/23			2/9			10/28			3/3			2/6	1/6			0/2			4/14			3/8		
%	50			69			35			22			36			100			33	17			0			29			37		
	57%						32%						42%							12%											

% for all motor 30/72 = 38%   % for all MMCV 50%
% for all sensory 14/27 = 52%   % for all MSCV 40%

1. V = Conduction Velocity
   A = Action Potential Amplitude
   L = Action Potential Latency
   CVSF = Conduction Velocity of Slow Fibres
   M = medium nerve
   U = ulnaris nerve
   P = peroneus nerve

2. Inconsistent results: significant increase in amplitude

3. % Ampl. = Proportion of the Amplitude
   An indirect measure of CVSF

4. Radial

5. In analysis of covariance

(mean ulnar CVSF 41.6 m/s), as the three higher blood lead ranges had higher conduction velocity means (43.0, 42.1 and 43.8, respectively), even though all of them were statistically different from the mean of the controls. Most of the significant differences in Seppalainen and Hernberg's (1982) study were found for the ranges 50-59 µg/dL or greater.

Bordo et al. (1982) also found significant differences at blood lead levels of 50-59 µg/dL, the abnormalities being more evident in workers with brief exposure and less significant in subjects with longer employment. This indicates a dynamic state during the early periods of exposure. The authors concluded that there was a possible threshold level of about 50 µg/dL. Baker et al. (1984) divided his worker group by blood lead level into four classes: 0-20, 21-40, 41-60 and 61-80 µg/dL. Motor amplitude changes started appearing at 41-60 µg/dL, whereas sensory changes were evident only in the highest group. The same variables (two motor amplitude, one sensory velocity and one sensory amplitude) correlated significantly with blood lead levels in the entire study group; age and other factors were adjusted for in the regression analysis. In Singer et al.'s (1983) study, subjects were grouped into < 40, 40-70 and > 70 µg/dL. A substantial increase in prevalence of nerve conduction abnormalities was noted between the two higher levels of exposure (25 versus 45%).

Four studies have imputed an effect at levels below 50 µg/dL. Seppalainen et al.'s (1979) findings have already been commented on. Seppalainen and Hernberg's (1982) paper would indicate an effect on nerve conduction after as early as 2 years but, as indicated earlier, we have some reservation in accepting their measurement of exposure. The paper by Bordo et al. (1982) implies a better definition of level of exposure except for their findings for the group that never had blood lead levels above 50 µg/dL. Examination of this group in terms of length of exposure showed the impairment to be absent in the workers with longest exposure. Such unexpected results have been interpreted as the consequence of a selection process or an indication of an 'unstable' neurophysiological situation in the early period of exposure. These changes may implicitly be reversible or represent a temporary dysfunctional reaction to the toxin. Rosen et al. (1983) divided their cases into three groups with blood lead levels of <30, 30-40, and >40 µg/dL. These were, however, the maximum lead levels within the past year, and the working period length ranged from 18-336 months in the low-exposure group to 29-312 months in the intermediate- and 6-318 months in the high-exposure group. It is not known how many of the individuals found with abnormalities had blood lead levels above 70 µg/dL in their previous employment period. On the other hand, Triebig et al.'s age matched pair analysis showed significant differences only for the group with blood lead levels above 70 µg/dL.

The findings presented above and the results of regression analyses conducted by some of the authors (Araki and Honma, 1976; Seppalainen, et al. 1979; Spivey et al., 1980; Rosen et al., 1983; Singer et al., 1983; Baker et al., 1984) indicate that the relationship between blood lead and impairment of peripheral nerve function would more likely take the form of a dose-response than a threshold effect. This still leaves the unresolved problem of the level at which blood lead will start to exert its toxicity. It seems logical that both the level of lead and the length of the exposure play a part, and possibly interact on the pathogenesis.

Conclusions

The clinical importance of slowed nerve conduction velocities which are still within normal limits in asymptomatic lead-exposed people with blood lead levels below 70-80 μg/dL is controversial. Those who regard slowed nerve conduction velocities as a sign of subclinical neuropathy argue that:

- axonal nerve damage has been shown in lead-intoxicated persons
- it only leads to slight decreases in nerve conduction velocities, as the remaining intact fibres are still able to conduct the impulse
- an increased proportion of abnormal nerve conduction parameters in lead-exposed workers is apparent in some studies (Table 2).

Opponents argue that:

- there is limited scientific evidence of the kind of pathological nerve changes in asymptomatic exposed individuals (nerve biopsies are unjustified in those cases)
- reliance upon animal studies is not possible, as animal species' susceptibility varies widely
- Buchthal's histological examination of a series of nerve biopsies of individuals with blood lead levels over 70 μg/dL revealed minor changes, not in the axon but in the axon membrane; this was interpreted as functional neuropathy (Rosen et al., 1983) due to "a minor defect in the excitable membrane of the nerve fibre" (Buchthal and Behse, 1979).

The following conclusions have been reached:

1) There seems to be sufficient evidence that blood lead levels under 70-80 μg/dL have been found associated with a slowing of nerve conductions.

2) It could not be determined whether there are any nerves or nerve conduction measurements that would be particularly sensitive to lead. It appears that lead does not selectively affect any particular peripheral nerve.

3) There seems to be some evidence, although not conclusive, that occupational low-lead exposure as indicated by blood lead levels as low as 30-50 µg/dl may affect nerve conduction.

4) There is some indication, although not conclusive, that a dose-response mechanism characterizes the relationship between blood lead levels and nerve conduction rather than a threshold effect.

5) The relationship between duration of exposure (long- and short-term) and nerve conduction impairment remains unclear. Minor changes in nerve conduction may be found very early. After 1-2 years, however, some studies seem to indicate that such changes tend to disappear unless there is a continued exposure to the toxin (Boothby and Rowland, 1974; Oh, 1975).

6) Whether the statistically significant findings are also biologically significant is controversial, particularly as the means of the nerve conduction measurements remain within the normal range, and the nature of the pathological nerve changes related to lead exposure is still not clearly understood.

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19. EFFECTS OF LEAD ON REPRODUCTION

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Introduction

Effects of lead on pregnancy have been known since the second half of the 1800's. In what is probably the first report in this field, Paul (1860) indicated the effect of high paternal lead levels on sterility, as well as on the viability of the conceptus. Several authors from a number of countries reported on the high risk to pregnancies for women employed in situations of high lead exposure (Rennert, 1881; Legge, 1901; Chyzzer, 1908; Oliver, 1911; Bourret and Mehl, 1966; Hamilton and Hardy, 1974). These reports showed increased risk of miscarriage, stillbirth and congenital anomalies, particularly macrocephaly. Women married to heavily exposed males were also reported to have a higher risk of miscarriage (Deneufbourg, 1905; Hamilton and Hardy, 1974). Koinuma (1926), in a case-control study conducted in Japan, reported that sterility was about double for workmen exposed to lead in a battery plant compared with controls (24.7 versus 14.8%); premature births and stillbirths were also much higher (8.2 and 0.2%, respectively). The effect of lead used to produce self-induced abortions was reported by Pindbourg (1945).

All these early reports indicated effects on reproduction at what must be considered high to very high levels of exposure to lead (i.e. above 80 µg/dL), but possibly also exposure to a series of other environmental contaminants, socio-economic and life-style characteristics that were not at that time considered important. Nevertheless, the reports also indicated the potential toxicity of lead, to both the reproductive system and the offspring, and they contributed to the implementation of preventive measures, including legislation in many countries forbidding the employment of women in lead industries (WHO, 1977).

More recently, the attention of investigators has shifted to the study of possible mechanisms and to the effect of lower exposure levels, partly because of the marked reduction in the body burden of lead in both exposed males and females. This review is concerned primarily with human data.

Animal Experiments

The extrapolation of animal experimentation results to humans is always fraught with difficulties. In the case of reproductive toxicity, extrapolation from animal data is further complicated because of the great differences in the effects produced by toxins on different species; a classic example is the teratogenicity of thalidomide, to which rats and mice are insensitive but rabbits and primates (including humans) are not (Shepard, 1976).

Experimental studies on the reproductive effects of lead exposure have been reviewed by Silbergeld (1983) and the US Environmental Protection Agency (EPA, 1986). There appears to be little doubt that high levels of lead are associated with spontaneous abortion and stillbirth in a variety of animal species, although these effects are not shown at lower levels. As well, effects toxic to the reproductive organs of adults and lethal or teratogenic to foetuses have been reported in animals fed high doses of lead (i.e. approaching overt toxicity).

At lower dosages (<5% lead acetate in drinking water), mutational effects on ovaries and sperm, decreased number of sperm, alteration of hormone chemistry and decrease in placental function are among the effects that have been noted. Teratogenic effects have been demonstrated only when lead was given by injection. Although the above results are not readily applicable to humans, they point to the necessity of following these leads and for monitoring the human population exposed to lead.

Effects on Humans

It is clear that placental transfer of lead (as well as other heavy metals) occurs in humans, and several studies have indicated a relationship between lead levels in maternal blood, cord blood, foetal blood and possibly placental tissue.

Wibberley et al. (1977) conducted a study of placental lead in Birmingham, comparing it with stillbirths, neonatal deaths and normal births. They found an increase in blood lead level corresponding to (i) malformed stillbirths and neonatal deaths (1.45 μg/g placental tissue), and (ii) neonatal deaths (1.73 μg/g) and stillbirths (1.45 μg/g) without malformations. Placental tissue values for normal births were 0.93 μg/g and for normal premature births 0.96 μg/g. These differences were not statistically significant. The authors suggested that the placenta may concentrate lead under stress situations in late pregnancy. Huel et al. (1981) examined the lead and cadmium content of hair of 110 mothers and their newborn at delivery. They found an inverse association between the cadmium content in baby hair and birth weight, and between the lead content in the mothers' hair and the gestational age of babies. Cadmium levels in babies of hypertensive mothers were three times as high as those in the hypertensive mothers themselves. These authors concluded that the placenta plays a more important role for cadmium than for lead.

Tsuchiya et al. (1984), in a larger study (231 deliveries), measured methyl mercury and several metals (total Hg, Mn, Cu, Zn, Fe, Cd, Pb) in maternal blood, cord blood and placentas, obtaining similar results: the intercorrelations between cadmium and lead were the strongest, both between levels in umbilical cord and placental tissues and between levels in maternal and cord bloods.

Alexander and Delves (1981) examined the blood lead from 165 pregnant women and 27 non-pregnant controls living in a rural area (Ashington, Northumberland), and in 19 pregnant women and 20 non-pregnant controls living in an urban area (Newcastle). They found no differences in blood lead levels between pregnant and non-pregnant women, but higher levels in the Newcastle sample for both groups. They also measured the blood lead levels of 23 neonates, finding them significantly lower than those of their mothers. They pointed out that the difference in blood lead levels of mothers in the two cities (15.7 µg/dL in Newcastle and 12.2 µg/dL in Ashington) was not accompanied by an increase in adverse perinatal events. The study is of interest because the blood lead levels are in the low range and closer to those likely to be found in non-occupationally exposed Canadian women. Angell and Lavery (1982), in one of the larger studies involving a total of 635 cases, examined the relationship between lead levels in maternal, infant and cord blood in 154 deliveries. They found the three measurements to be highly correlated.

Recently, Thompson and Robertson (1985) reported on the possibility that increased mobilization of lead stores from bone during pregnancy may give rise to an additional reproductive hazard in women with past high lead exposure.

Lead in the milk of lactating women has also been found to correlate with their blood lead levels, although Rockway et al. (1984) calculated that daily ingestion of lead for infants which are breast-fed was very low (about 2 µg/day), considering an absorption factor of 50%. The authors admitted that the level of lead found in breast milk in their population was lower than had been found in other studies.

Kovar et al. (1984) measured lead (and cadmium) in the breast milk of 28 mothers in London; the mean concentration of lead in breast milk was found to be 2 µg/dL, about one-half the concentrations found in two brands of commercially prepared formulas. They also concluded that the risk to the health of the infants from excess lead (or cadmium) from breast-feeding is quite small. More recently Rabinowitz et al. (1985) reported on lead levels in 100 samples of breast milk from a Boston hospital. Lead levels averaged 1.7 µg/dL, marginally below the 2.3 µg/dL average found in three brands of formula milk. The authors' conclusions confirmed that the low levels of lead found in breast milk gave no cause of concern as to the health of breast-fed babies.

Infants' burden of lead is influenced by maternal blood lead in two ways. Lead crosses the placental barrier and gets into the cord blood, where the concentrations are somewhat lower than those found in maternal venous blood. In recent studies such levels averaged 5-8 µg/dL. Breast-fed infants also ingest lead contained in their mothers' milk, where concentrations are generally be very low (around 2 µg/dL), lower than the amount reported in commercial milk formulas.

Although in some areas of Scotland there has been concern that milk formulas reconstituted with water that contains high concentrations of lead may be a problem, at the low level found in breast milk and commercial milk formulas lead does not seem to constitute a 'health risk' to infants.

Effects of Pre-natal Lead Exposure on the Newborn

Case Reports

Pearl and Boxt (1980) described the results of a radiographic examination on a full-term asymptomatic child born with congenital lead poisoning secondary to maternal pica. They reported lead lines and a dense cranial vault, as well as delayed skeletal and dental development at birth. After chelation at age 6 months, the X-ray showed normal skeletal maturation; tooth eruption, however, did not occur until 15 months of age. Bony changes were also reported by Sensirivatana et al. (1983) in a case of lead encephalopathy in a 2-month-old child with a blood lead level of 112.9 µg/dL. The father's and mother's blood lead levels were much lower (32.3 and 24.2 µg/dL, respectively), but the child was found to have extremely high levels of lead under the nails.

An increase in chromosomal breakage was found at the eighth month of pregnancy in the amniotic fluid of an infant exposed to a high level of lead (90 µg/L) (Qazi et al., 1980). The baby was born 8 days after chelation of the mother. The increase, consisting of gaps, chromatid and chromosomal breaks, was temporary and no longer visible after 3 months; the EDTA chelation of the mother before birth may have been responsible for the observed effects. A case of congenital lead intoxication with seizures has also been reported by Ghafour et al. (1984). The child's blood lead level was as high as 81 µg/dL at 17 days of age, when the baby was chelated and the seizures disappeared. The authors noted that at 16 months the infant looked clinically normal, but at 2 years of age a basic developmental screening test showed poor language development. Palmisano (1969) reported the case of a 10-week-old infant with evidence of neurological defects, intra-uterine growth retardation and post-natal failure to thrive.

Greenfield (1957), on the other hand, described the case of a woman with plumbism who became pregnant and had a normal baby. Her blood lead level during pregnancy was about 100 µg/dL. Another woman with overt lead poisoning (blood lead level 240 µg/dL), 8 months pregnant, was described by Angle and McIntire (1964). She received EDTA chelation therapy for 7 days. One month after this treatment, she delivered a healthy baby weighing 3200 g; follow-up 1 year later revealed normal development. A similar case was described by Abendroth (1971). Following chelation therapy, this patient also had a healthy baby who was reported doing well 4 months after delivery.

These cases confirm the strong likelihood of toxic effects from high maternal levels of lead on the newborn, but also seem to indicate that the effects may be reversible.

Epidemiological Studies

Fahim et al. (1976) measured maternal blood, cord blood, placenta and membrane tissues for lead, copper and zinc in women (n = 502) from two places near the lead belt area of Missouri. They compared the lead levels for those with normal term delivery with those who were delivered pre-term or had premature rupture of the membranes (PROM). In both localities lead levels in maternal and cord blood were lower for normal term deliveries than for preterm deliveries and PROM's. The mean levels (in µg/dL) were 13.1, 30.1 and 26 for Columbia, and 14.3, 25.6 and 25.9 for Rolla, respectively. The affected groups showed a similar increase in concentration of lead in the membrane. Copper and zinc did not show any difference. Some reservations with respect to the analytical chemistry aspect of this study were expressed by Clark

(1977), who himself compared 122 children from a mining town in Zambia with 31 controls from another area where there was no lead exposure, the mean blood lead level of the mothers being, respectively, 41.2 and 14.7 µg/dL. No differences were found in birth weight, hemoglobin and hematocrit.

A series of studies on the health effects from a smelter industry was conducted in northern Sweden by Nordstrom et al. (1978) in and around a smelter that produces copper, lead and other metals and chemicals. They found that infants from females employed in the smelter in the past had lower birth weights that were related to (i) employment of mother in the smelter during pregnancy, (ii) the distance that the mother lived from the smelter, and (iii) the proximity of the mother's job to the actual smelting process; the weight decrease was noted particularly in later pregnancies, i.e. after the second-born. Similar associations were found for the number of spontaneous abortions (Nordstrom et al., 1979a). Abortion data were collected for all women born after 1930; even with the most conservative estimate of the fertility age, the time span covered is quite long and most likely heterogeneous as to the type and amount of emissions. These authors (Nordstrom et al., 1979b) also studied birth defects for the period 1955-76, and concluded that the frequency of single and multiple malformations increased with the proximity of the mother to the smelter during pregnancy. In addition to the lack of control for socio-economic and mothers' life-style factors, the fact that the population sampled was exposed to a multiplicity of toxic substances including arsenic, mercury, cadmium and sulphur dioxide makes the association with lead a putative one.

Another study on spontaneous abortion was conducted in Finland by Hemminki et al. (1980). They analysed the ratio of spontaneous abortions to live births among female metal workers in various industries compared with all Finnish women. The authors found the ratio to be higher for all union members (all metal industries combined)--13.79 compared with 10.34 for all Finnish women. The increase seems to result in large measure from females employed in production of electronic equipment, radios and television sets, a group for which the differences were statistically significant. Higher ratios were found as well for women engaged previously in metal mining and forming. The authors proposed that fumes from solder may possibly be responsible for the higher rates.

In a study of over 4000 deliveries at a hospital in Boston, Needleman et al. (1984) found that cord blood lead levels were positively associated with minor anomalies (hemangiomas, lymphangiomas, hydrocele, minor skin defects and undescended testicles). No particular defect was associated with the lead levels, which ranged between 8.7 and 35 µg/dL. Although the authors noted that minor defects could be 'markers' for more serious defects, there was no significant relationship with any of the major defects. They also found a significant negative association between lead and first trimester bleeding, premature labour and neonatal respiratory distress; these findings raise the possibility of random variation or of the influence from an unknown variable. Mothers with higher lead levels were significantly more likely to be on welfare, to have less college education, to smoke and to drink more coffee and alcohol. These and other confounding variables were taken into account by logistic regression analysis. Additionally, the problem of multiple comparisons must be considered in relation to statistical significance.

Evidence of the possible role of chronic lead exposure, likely prenatal, also comes from Beattie et al. (1975), who measured water and blood lead levels in 77 mentally retarded children aged 2-6 years and 77 matched controls. Both water and blood lead concentrations were higher in the retarded group.

In the previously mentioned study of 635 deliveries, Angell and Lavery (1982) found no relationship between lead concentrations in cord blood with PROM, pre-term delivery, pre-eclampsia or meconium stain. Only two women had blood lead concentrations higher than 25 µg/dL.

Khera et al. (1980) reported on placental lead levels in occupationally exposed women in the United Kingdom. They found that lead levels correlated with duration of employment and increased with maternal age independently of duration of employment. There was no relationship with stillbirths, although placental lead in 20 stillbirths of occupationally exposed mothers was higher than those found in the 8 stillbirths of mothers not so exposed. Variation in the lead levels of placentas from their previously reported work (Wibberley et al., 1977) and from the results of other authors makes interpretation of this study difficult. Roels et al. (1978) reported no correlation between placental lead concentrations and birth weight in a variety of locations in Belgium, but Karp and Robertson (1977) reported an association of placental lead with decreased activity of the placental enzyme, steroid sulphatase. However, they found a similar association with mercury, so that either metal could be blamed.

Bryce-Smith et al. (1977) and Khera et al. (1980) produced evidence of some increase in lead levels in bone samples for stillborns. In the Bryce-Smith et al. study, cadmium in stillborns was also found to be substantially higher in comparison with accident cases. These findings raise the question of possible confounding effects from several heavy metals.

Saric (1984) found the rate of spontaneous abortion between 1961 and 1980 to be 15% in a community with a lead smelter compared with 7% in a control community. No blood lead levels were offered to confirm exposure, however, and the number of abortions was cumulated for the entire 20-year spread, making interpretation difficult. It is also impossible to reach a meaningful conclusion from this study because rates are calculated on the basis of 1000 inhabitants; miscarriage rates (or more appropriately ratios) should be calculated per live births in order to ensure comparability.

Most of the literature relating to antenatal lead exposure at low levels deals with neurobehavioural changes, and this has been discussed elsewhere. A recent article (Ernhart et al., 1985a) reports on a study of newborn-mother pairs conducted in Cleveland, Ohio. Blood lead levels ranged between a mean of 6.2 for white and 6.8 µg/dL for black maternal blood; cord blood was found to have a mean lead level of 5.7 and 5.8 µg/dL, respectively (Ernhart et al., 1985b). In all, 17 neonatal measurements were taken, including APGAR scores, growth retardation, neonatal anomalies and 10 newborn neurological and behavioural measurements. When the scores were related to maternal and cord blood lead levels, three of the neurological measurements where found to be significantly related to one or the other of the blood lead measurements but not to both, this notwithstanding a correlation of 0.80 between maternal and cord blood. Upon reanalysing with an increased number of pairs to overcome variations in sampling, only one measure (neuro soft-signs) retained a statistically significant ($p = 0.035$) association with maternal but not cord blood lead levels.

Sudden Infant Death Syndrome (SIDS)

Hoppenbrouwers et al. (1981) drew attention to lead in the air when examining the seasonal relationship between SIDS and environmental pollutants. There was a close relationship between monthly levels of carbon monoxide and lead levels in the air, the highest levels being observed from November to January. They found that SIDS cases in Los Angeles County followed temperature, barometric pressure and monthly lead levels, with a time lag of 7 weeks. The authors concluded that "because of its neurotoxicity lead deserved a further scrutiny as a predisposing factor in risk for SIDS".

The possibility of a relationship between SIDS and prenatal exposure has been recently explored by Erickson et al. (1983), who studied the tissue levels of several elements in lung, liver, kidney and rib tissues of 66 autopsies of SIDS infants and 23 infants who died suddenly from other causes. They found an increased lead content in the liver and rib of the SIDS infants ($p < 0.05$ and < 0.01, respectively). Cadmium levels were also higher in liver and rib tissue, but the differences did not reach statistical significance. Other tissue levels were found to be within the expected range. Other known exposure factors relevant to SIDS, such as mothers' smoking and drinking habits, could not be examined in the study, and the authors concluded that the higher lead levels found in the SIDS infants did not provide evidence of lead toxicity.

Lyngbye et al. (1985) examined the dentine content of 1302 first-grade children in Aarhus, Denmark, as part of a lead screening programme. Families of 101 children in the higher 8% of tooth lead concentrations were matched with those of children with the lowest concentrations. Families were interviewed by a pediatrician blind to lead data. Three cases of 'near miss' SIDS (ages 11 days, 12 days and 8 months) were found among the high-lead-level groups and none among controls. In two of the cases, one of the parents was occupationally exposed. Lead levels were measured in teeth about 6 years after the event, and additional maternal factors of risk for SIDS were not considered. No clear relationship between lead exposure and SIDS was demonstrated in any of the above studies.

Effects on the Fertility of Men

Mattison (1983) reviewed the mechanisms of action of reproductive toxins, indicating that they may act directly or indirectly. The direct effect occurs either because of chemical reactivity (e.g. destruction of germinal cells by alkylating agents) or because of structural similarity to endogenous compounds such as hormones or nutrients. The indirect action may require metabolic processing before the toxin can exert its action through one of the above direct mechanisms; alternatively, the toxin may alter some physiological control mechanism by induction or inhibition of certain enzymes. Most reproductive toxins are species-specific, i.e. they may be toxic in one species (including humans) and not in another. Their toxicity may depend on the time at which the exposure occurs, and the stage of development of the particular target organ may be particularly important. Gender differences are also well known (Doull, 1975).

Because of the easier accessibility of male gonads and gametes for morphological studies, researchers have been focussing particular attention on male fertility.

Stofen (1974) reviewed the data from Neskov who, in an early, uncontrolled study in the USSR, examined 66 workers exposed to leaded gasoline (organic lead). In 58 of these workers there was a decrease or disappearance of erection, in 41 early ejaculation and in 44 a decrease in the number of spermatocytes. No indications were offered as to the levels of blood lead, and the possibility that other chemicals in gasoline may have been responsible for the effects cannot be ruled out.

Lancranjan et al. (1975) reported on 150 men occupationally exposed to lead. They grouped the men into four categories according to their mean blood lead levels (74.5, 52.8, 41 and 23 μg/dL). Despite apparent overlapping of the categories, there was a steady increase in the proportions of asthenospermia, hypospermia and teratospermia; other measurements of infertility were not found to be reliable. Seventeen of the subjects in the higher exposure groups had been chelated with EDTA.

In the continuing search to determine the sites at which lead may affect the male reproductive system, Braunstein and co-workers (1978) conducted a comprehensive examination of the hypothalamic-pituitary-testicular axis on 10 men with occupational exposure, 6 of whom had clinical signs of poisoning. Mean highest blood lead level for the lead-poisoned men was 88.2, 80 for the four exposed men and 16.1 μg/dL for the nine controls. At the time of examination the blood lead levels were 38.7, 29.0 and 16.1 μg/dL, respectively; all the exposed individuals had been treated with EDTA. Decreased libido and frequency of intercourse were present in nine of the workers and only one of the controls. The two most severely leaded workers underwent testicular biopsy: peritubular fibrosis and oligospermia were the main findings. Oligospermia was found in semens of four of the eight workers that could be tested. Serum testosterone, oestradiol, testosterone-oestradiol binding activity, luteinizing hormone and follicle-stimulating hormone were tested before and after stimulation. A decrease of serum testosterone levels was found in both high-lead groups, although the response to human chorionic gonadotropin was normal. There were no differences in the basal levels of the other hormones tested; however, the lead-poisoned (but not the other lead-exposed) men had a significantly decreased increment in serum luteinizing hormone following clomiphene administration. The authors concluded that lead poisoning may affect the reproductive system at both the hypothalamic and testicular levels. They could not, however, discount some effects from EDTA treatment.

Butrimovitz et al. (1983) attempted to establish whether concentrations of lead in the semen might represent a more accurate index of reproductive exposure to lead than blood concentrations. They examined the quality and the number of sperm in 16 vasectomized men and 21 normal controls with no history of lead exposure. Seminal lead concentrations were extremely low at 3.8 µg/dL ± 1.5 (SD) for the controls and 4.1 µg/dL for the cases. There was no correlation between seminal lead levels and sperm motility or sperm counts.

Stanwell-Smith et al. (1983) compared blood lead, zinc, copper and cadmium levels in 80 infertile men and 38 controls. A significant ($p = 0.01$) increase in plasma copper concentration was found in the infertile men (1.5 µmol/L). No differences were found for blood zinc, lead and cadmium levels. Infertiles with antisperm antibodies or counts above 20 million/mL exhibited higher seminal plasma zinc.

Dawson et al. (1985a) reported on a study of lead, cadmium and aluminum content of seminal plasma in 64 apparently healthy men separated into three groups according to live sperm counts. They found significant differences between the high and low live-sperm groups for lead ($p < 0.001$) and aluminum ($p < 0.05$). Regression analysis showed an inverse correlation between sperm counts and the two metals ($p < 0.001$ and $p < 0.01$, respectively). In another study (Dawson et al., 1985b), the authors compared 10 azospermic men with 20 subjects with normal sperm. They found significantly higher seminal plasma levels of lead, cadmium and aluminum in the azospermic subjects, and were able to ascertain that lead ions are secreted by the prostate into seminal plasma whereas cadmium and aluminum are probably secreted by the seminal vesicles.

Cullen et al. (1984) studied the hormonal and reproductive functions of seven cases referred to hospital with symptomatic occupational lead intoxication and blood lead levels ranging from 66 to 139 µg/dL. Among six nonvasectomized individuals, three had defects in spermatogenesis, two had azospermia and two (one a diabetic) had oligospermia. They all had normal serum testosterone. As with all case studies, because of the absence of controls, the selection problems and the possible presence of confounding conditions, the authors could not impute their findings to lead exposure.

Although the results presented in some cases are contradictory, there is little doubt that several heavy metals, including lead, can affect the male reproductive system, particularly at toxic doses. The case is not so clear for blood lead levels below 40 µg/dL. In most of the studies, the majority of which have been conducted on occupationally exposed workers, it has not been possible to account for confounding variables (e.g. socio-economic factors, drinking habits), coexisting conditions (e.g. urinary tract and venereal infections, affections of the prostate or endocrine dysfunctions) and the ubiquitous presence of other toxicants, all known to be capable of causing similar effects. This in itself does not deny the veracity of the findings reported, but it makes it very difficult to impute a direct (cause-effect) involvement to lead, in particular at the levels at which general populations are exposed.

Mutagenic Effects

Lehnert (1970) studied German workers with high blood lead concentration (62-89 μg/dL). He found an increase in chromosomal gaps and breaks and a positive correlation with increased urinary δ-aminolaevulinic acid (ALA) and the percentage of mitoses observed.

Forni and Secchi (1972) examined 77 workers exposed to lead and 65 non-exposed workers. They classified the workers as (i) clinically poisoned (mean blood lead 77.3 μg/dL, n = 37), (ii) pre-clinically intoxicated (64.07 μg/dL, n = 15), and (iii) no longer exposed for at least 18 months (55.6 μg/dL, n = 13). Compared with the controls, there was a significant difference in chromatid aberrations and unstable chromosomes for the first two groups but not for the no-longer-exposed group.

Deknudt et al. (1973) reported on a study conducted on 14 workers from a zinc industry who had presented warning signs of lead poisoning. They subdivided the sample into three groups according to levels of contamination in the dust: Group I--high zinc but low lead and cadmium (n = 5); Group II--high zinc, lead and cadmium (n = 5); and Group III--high lead and cadmium but no zinc (n = 4). The three groups were also compared with five from exposed controls. The results indicated an increase in all cytological abnormalities for the three groups combined compared with controls. The findings are difficult to interpret: the percentage of cells with chromosome or chromatid aberrations, dicentric and acentric cells and the number of gaps per cell were found highest in the group with high zinc, the next highest being the group with high lead and cadmium. The results are, therefore, unclear but, because all the workers had suffered from lead poisoning, the authors concluded that the findings were due chiefly to lead.

O'Riordan and Evans (1974) examined 70 workers in a ship-breaking yard. They found no difference in chromosomal aberrations between 35 yardworkers exposed to lead oxides (burners) and the non-exposed workers (non-burners) when compared with the general population. There were no differences in chromosomal analyses among blood lead level categories (<40, 40-80, 80-120, >120 g/dL) nor according to job categories. They did, however, find a significant difference in chromosomal breaks and gaps in all shipyard workers when compared with their general population controls.

Schwanitz et al. (1975) studied the rates of secondary chromosomal aberrations in 105 subjects with varying degrees of exposure to lead. Blood lead levels ranged from 11.6 to 98 µg/dL. No significant correlations were found between lead content in blood, ALA excretion in urine and cytogenetic findings. The rate of cells with chromosomal aberrations for the group was slightly increased (14.1%) compared with that expected in the general population.

Forni et al. (1976) looked at the initial effects of occupational exposure to lead, making serial determinations in 11 subjects for 18 months. Chromatid and one-break chromosomal aberrations doubled after 1 month and increased further for 2 months. After a relatively steady period (up to 7 months), the number of aberrations tended to decline. Blood lead levels increased from 34 to 56 µg/dL over the first 3 months, then levelled off. The ALA activity of red blood cells exhibited a similar pattern. Forni et al. (1976) thought that these three trends indicated the possibility of a compensatory mechanism.

Bauchinger et al. (1976) compared 24 workers with increased levels of lead and cadmium with 15 controls. They found an increase in chromatid damage (single breaks and exchange) accompanied by acentric fragments. Lead levels were in the low range (19.3 and 12.5 µg/dL averages for cases and controls, respectively), whereas cadmium differences were more substantial (0.395 and 0.150 µg/dL, respectively). Because of the exposure to lead and zinc, the authors could not attribute the mutagenic effect to cadmium alone.

Deknudt et al. (1977) compared the proportion of chromosomal aberrations found in workers exposed to lead: 16 cases in Lyon with blood lead levels of 95 µg/dL, 7 in Nerem for which blood lead level was not available but who had elevated urinary ALA or coproporphyrin excretion, and 20 controls. They found an increased number of severe aberrations (rings and dicentrics) in the Lyon subjects but not in those in Nerem who had, however, an increased number of fragments. The workers from Lyon had very high levels of lead in their blood, ranging from 44.5 to 95.2 µg/dL, but no relationship was found between blood lead levels and the number of aberrations, whether severe or not. The authors indicated the possibility of an effect from subclinical calcium deficiency or from zinc and other heavy metals.

Bauchinger et al. (1977) reported on chromosome analyses conducted on 20 children living in a town with a lead plant (mean blood lead levels 29.0 µg/dL) and compared them with 20 controls, 10 from 20 suburbs (mean = 13.2 µg/dL) and 10 from an island (mean = 11.8 µg/dL). No relationship was found between the number of cells with chromosome damage (both unspecified and structural) and the number of gaps per cell, despite the significant difference in blood lead levels.

Garza-Chapa et al. (1977) compared 44 workers exposed to lead oxide with 15 controls--the mean blood lead level in the workers was found to range between 30 and 75 μg/dL (mean = 30.7), and that of the controls ranged from 15 to 35 μg/dL (mean = 15.3). They found an increase in breaks and gaps and chromosomal aberrations, in relation to both duration of exposure and blood lead levels ($p = 0.01$). It is of interest to note that three controls and seven workers were examined a second time after an interval of 3 weeks; the differences in these categories of chromosomal abnormality decreased substantially and became insignificant. While pointing out the small number of workers retested, the authors concluded that longitudinal observations may be the best way to study chromosomal aberrations in exposed individuals.

Nordenson et al. (1978a) reported on an increased frequency of chromosomal aberrations found in workers exposed to lead for the same smelter areas as reported before, the rates being 11.2 per cell for six individuals with lead levels about 50 μg/dL, 7.4 per cell for those with levels between 25 and 50 μg/dL and 6 per cell for those found to be below 25 μg/dL. The abnormalities found to differ significantly were gaps and chromosomal aberrations. It is of interest to note that, in the previous year (Nordensen et al., 1978b), they had made similar observations in the same areas that were correlated with arsenic, and suggested an interaction of arsenic with smoke. In the lead study, a significant association was found with chromatid aberrations. Interaction with smoking appears to be a common factor.

Sarto et al. (1978) reported on 20 occupationally exposed men and 20 controls matched by age and chosen among blood donors. The mean blood lead level for the workers was 71.9 μg/dL (range 50-100 μg/dL). The increase of chromatid and chromosomal aberrations among the cases was almost threefold compared with the controls ($p < 0.001$). The most frequently found aberrations were gaps (correlation with blood lead level $r = 0.53$). Dicentric chromosomes were found in two cases and none of the controls. Stable aberrations (dicentric and non-coupling chromosomes) were found in nine of the cases compared with only two of the controls. The authors concluded that lead is capable of mutagenic effects.

Forni et al. (1980) conducted a study on female workers. The authors compared 18 healthy females occupationally exposed to lead (mean blood lead levels 42.0 µg/dL) with 12 female controls (mean 27.8 µg/dL). The results showed a significant increase in the rate of metaphases with chromatid and chromosomal aberrations, excluding gaps, for the exposed groups. Aberrations were measured after 48 and 72 h of culture. Whereas both groups showed an increase in the rates of aberrations in the later cultures, this increase was significantly more marked for exposed females. The authors concluded that it is likely that the aberrations observed in lymphocyte cultures in lead-exposed subjects may be culture-borne aberrations which cannot repair in the presence of lead or of some metabolite, induced by lead, that accumulates with time.

Another study on long-term lead-exposed men was reported by Grandjean et al. (1983). The men showed a significant elevation of zinc protoporphyrin (ZPP). Their blood lead levels ranged from 29.0 to 74.5 µg/dL. Lead levels and zinc ZPP correlated with average number per cell of sister chromatid exchanges (SCE) ($p < 0.05$ and $p < 0.001$, respectively). Four weeks after cessation of exposure, the SCE rates decreased significantly. Newly exposed workers did not show any increase in SCE despite increased ZPP after 4 months.

The relationship between lead exposure and mutagenic effects on human lymphocytes remains controversial. In the better-conducted studies, evidence has been found of an association between blood lead levels and chromatid and chromosome damage, mostly of the minor types. The results from larger studies and studies in which more than one metal was measured are more contradictory. Several studies show the likelihood of the changes being reversible. Generally, cytological studies have been conducted 'in isolation', without taking into consideration other medical conditions, other exposures (e.g. medical X-rays) and personal habits (such as smoking), again making it difficult to impute a 'causal' role to lead.

Conclusions

The evidence from animal experiments and human studies leaves little doubt that exposure to high levels of lead has important reproductive effects. It is much in doubt, however, whether such effects occur at lower exposures, such as those of the majority of the Canadian population (blood lead level <20 μg/dL). The evidence at such low dosages becomes less consistent, in both human observations and animal experiments, and the effect of possible confounders such as exposure to other toxic metals, life-style habits and socio-economic situations increases substantially. We must agree with the opinion expressed by the US Environmental Protection Agency that well-designed epidemiological studies involving a large number of subjects are needed to clarify the relationship.

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20. THE RELATIONSHIP BETWEEN BLOOD LEAD LEVELS AND BLOOD PRESSURE*

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Concerns about the health effects of ambient exposure to lead traditionally have focussed on children. Although lead has a variety of adverse effects on the health of adults, most of them appear not to be of substantial concern except at very high blood levels. Recently, however, two new and extensive analyses of the NHANES II data set have shown a strong and robust relationship between blood lead levels and blood pressure. That finding has important implications for the benefits of reducing lead in gasoline because high blood pressure, in turn, is linked to a variety of cardiovascular diseases.

This review analyses the experimental and statistical relationship between blood lead level and blood pressure. The first part provides a brief overview of the experimental and epidemiological studies previously done, and the second part provided a detailed discussion of the recently completed analysis of the NHANES II data.

Earlier Studies

Epidemiological Studies

Lead has long been associated with effects on blood pressure and the cardiovascular system, including a study by Lorimer in 1886 that found that higher blood lead levels increased the risk of hypertension. Most of the studies have focussed only on hypertension and relatively high lead exposure levels, and have not looked for a continuous effect of lead on blood pressure. Investigators reporting such an effect include Beevers et al. (1980), Morgan (1976), Richet et al. (1966) and Dingwall-Fordyce and Lane (1963). Others have failed to find effects of lead on hypertension that were significant at the 95% confidence level, although most of them did find a positive association. These include Ramirez-Cervantes et al. (1978) and Fouts and Page (1942).

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More recently, Batuman et al. (1983) found an association between chelatable body lead levels and hypertension in veterans, and several recent general population studies and lower lead exposure studies (Beevers et al., 1976; Kromhout and Coulande, 1984) have found a significant association with blood lead level. Khera et al. (1980) compared blood lead levels of hypertensive and cardiovascular patients with those of hospital controls in Birmingham, England, and found that blood lead levels were 55% higher in the patients with hypertension and ischaemic heart disease. Moreau et al. (1982) also found a significant relationship ($p < 0.001$) between blood lead levels and a continuous measure of blood pressure in 431 French policemen, after controlling for age, body mass index, smoking and drinking.

An even more recent British study (Pocock et al., 1984) found blood lead level significantly related to blood pressure at the 99% confidence level, but the authors felt that the small size of their correlation coefficient suggested no noticeable effect. However, that conclusion appears to reflect a misunderstanding of statistics. It is the regression coefficient that indicates the size of an effect. A correlation coefficient confounds that measurement with the variances of the dependent and independent variables. Although their full data set was not available to us, Pocock et al. (1984) presented their grouped data, and we were able to perform a regression of blood pressure versus the log of blood lead level on their group averages, both before and after adjustment for confounders. The regressions were weighted by the inverse of the variance of each group, and confirmed their finding that blood lead level was a significant predictor of blood pressure in their data, both before and after adjusting for covariates. Moreover, the regression coefficient indicated that the size of the effect was significant, suggesting a change of 3 mmHg (the standard measure of blood pressure) as blood lead level goes from 5 to 15 µg/dL.

Wedeen et al. (1975) found lead associated with the vascular renal changes linked to essential hypertension, indicating a possible causal pathway. Cooper and Gaffey (1975) analysed mortality data from 1267 death certificates for 7032 lead workers employed between 1900 and 1969, and found a significant excess of deaths from hypertension disease and renal disease. A later analysis of similar data from 1971 and 1975 also found an increase in cardiovascular and renal disease, but it was no longer significant at the 95% confidence level (Cooper, 1981). A more recent analysis by Cooper (1984) found SMR's of 128 and 203 for hypertensive heart disease in battery plant and smelter workers, respectively, and of 320 and 475 for other hypertensive disease. Voors et al. (1982) found tissue lead level to be associated with cardiovascular deaths ($p = 0.0021$) in an autopsy study in North Carolina, after controlling for cadmium and age. Lead explained 11.8% of the variation in the proportion of deaths due to cardiovascular disease.

The direct cardiological effects of lead are also indicated by electrocardiogram changes in lead-poisoned children, which are reversed by chelation therapy (Freeman, 1965; Silver and Rodriguez-Torres, 1968). Williams and coworkers (Williams et al., 1977, 1978; Williams and Hejtmancik, 1979) showed persistent increased susceptibility to norepinephrine-induced arrhythmias in rats exposed to lead in the first 3 weeks of life.

Experimental Evidence: In Vivo Studies

A considerable body of experimental evidence indicates that low to moderate doses of lead increase blood pressure in animals by increasing the resting tone (tension) of the vascular smooth muscles. Victery et al. (1982) found lead associated with a significant elevation of blood pressure in rats with blood lead levels of 41 µg/dL. Importantly, this study confirms Beevers et al.'s 1976 finding of a sex differential, with male rats showing a more pronounced rate. Webb et al. (1981) also found that rats fed lead had significantly higher blood pressure; they then examined the vascular responsiveness of tail arteries in rats exposed to blood lead levels in the 40 µg/dL range that had suffered increases in systolic blood pressure, and found that the arteries in exposed rats had increased contraction in response to stimulation by neuro-transmitters.

Iannaccone et al. (1981) also reported increased blood pressure (p 0.001) in rats at blood lead levels of 38.4 µg/dL, as well as significant increases in the blood pressure response to noradrenalin. Perry and Erlanger (1978) found that low-level exposure of rats to lead produced increases of 15-20 mmHg in systolic blood pressure. Kopp et al. (1980) repeated those studies and found electrocardiogram changes, indicating an effect on the heart itself. Subsequent tissue analysis of the heart showed reduced levels of ATP in the heart muscle, indicating that heme synthesis inhibition by lead was affecting energy availability in the heart itself.

Carmignani et al. (1983) measured both systolic and diastolic blood pressure and found that lead increased both measurements. They also found increased reactivity to alpha-adrenergic stimulation, confirming the results of Webb et al. (1981) and Iannaccone et al. (1981). In addition, Revis et al. (1981) demonstrated increased blood pressure in pigeons fed 0.8 ppm lead acetate in drinking water. Thus experiments by several groups, using two different animal species, have shown that lead increases blood pressure.

Experimental Evidence: In Vitro Studies

Webb et al. (1981) reported that when helical strips of the smooth muscle lining the tail arteries of lead-exposed and controlled rats were compared, the lead treated tissue manifested increased contractile response to alpha-adrenergic stimulation, confirming the *in vivo* results of Iannaccone et al. (1981) and Carmignani et al. (1983). Piccinini et al. (1977) and Favalli et al. (1977) placed whole arteries from rats not previously exposed to lead in a supporting medium and demonstrated that, when lead was infused into the medium in concentrations ranging from 5 to 15 μmol/L, there was a dose-dependent contraction of the arterial muscle, restricting the flow of fluid through the artery. They also found that lead disturbed the calcium metabolism of the arterial tissue, resulting in increased intracellular calcium stores and increasing the sensitivity of the muscle to extracellular calcium concentration, suggesting a disturbed ability to keep extracellular calcium out of the cytosol.

Lead, Cellular Calcium Metabolism and Blood Pressure

It has long been known that hypertension is linked to increased resistance to blood flow, due to reduction in the radius of the arterioles. Other research has implicated changes in the tone of the smooth muscle as a principal factor in that constriction. The obvious question is whether lead fits into this picture in a coherent way.

Because lead is a divalent cation and capable of interfering in calcium metabolism, interference in calcium metabolism is an obvious possibility. Indeed, Aub et al. (1926) remarked that "lead follows the calcium stream," indicating that the lead-calcium association is a long-recognized one. And examining the role of calcium metabolism in blood pressure and the role of lead in calcium metabolism reveals a picture that is consistent with the available experimental and epidemiological data.

Calcium plays a complex role in both the responsiveness of arteriolar smooth muscle to stimuli and its steady-state contractile activity (tone). The multitude of interactions between lead and calcium metabolism suggests that lead may interfere with almost all of those processes.

The basic points that will be discussed are as follows:

1) Increased intracellular calcium leads to increases in the tone of the smooth muscles lining the arterioles. This appears to be important in hypertension. Indeed, the FDA's recent approval of calcium channel blockers for the treatment of hypertension demonstrates the recognized importance of intracellular calcium in regulating blood pressure.

2) Although there is considerable disagreement among researchers on the relative importance of the many factors affecting intracellular calcium concentrations, among the pathways considered important by some researchers are the sodium-potassium pump, the calcium pump and uptake by the endoplasmic reticulum and mitochondria. Cyclic-AMP (cAMP) plays a role in stimulating the calcium pump and in modifying the calcium-stimulated activity of myosin light-chain kinase (MLCK).

3) Lead has been shown to increase intracellular calcium in vascular smooth muscle, as well as hepatocytes, osteocytes and neurons.

4) Lead has been shown to inhibit Na/K-ATPase activity in erythrocytes and neurons, to increase stores but reduce uptake rates for calcium in the endoplasmic reticulum and the mitochondria, and to activate the enzyme system that produces hydrolysis of cAMP.

5) Lead-induced changes in smooth muscle tone are consistent with its interference with calcium metabolism.

Calcium Metabolism, Smooth Muscle Tone and Blood Pressure

A somewhat simplified picture of the role of calcium in smooth muscle is described below (see Rasmussen (1983) for more details). The contraction of the smooth muscle is mediated by an increase in cytosolic calcium, although the exact sources of the calcium are not known. This increase in free ionized calcium leads, via calcium-calmodulin, to an activation of MLCK, which phosphorylates myosin light-chain resulting in increased cross-bridging activity and increased muscle tension.

Meanwhile, the cell acts to restore cytosolic calcium to normal by promoting calcium efflux across the plasma membrane, through the calcium pump and, perhaps, via sodium-calcium exchange through the sodium-potassium pump. Calcium is also taken up by the sarcoplasmic reticulum and possibly mitochondria, again reducing cytosolic free calcium stores. In addition, the contractile response is controlled and attenuated by a cAMP-dependent protein kinase which, by phosphorylating the MLCK, reduces its activity.

The steady-state tone of vascular smooth muscle is due to a cytosolic calcium content above the threshold for contraction. This results from a balance between efflux and influx across the plasma membrane. This makes it extremely sensitive to anything that disturbs the ionic balance in the cell; indeed, Filo et al. (1972) showed (*in vitro*) that smooth muscle tension exhibits a steep, logistic-shaped dependence on free calcium concentration in the cytosol.

Although the specific mechanisms implicated in essential hypertension are still in dispute, it is interesting to note in this regard that Bruschi et al. (1985) reported that cytoplasmic free calcium in the platelets and lymphocytes of people with essential hypertension was 10% higher than in the control group. A similar but somewhat larger difference was seen in the spontaneously hypertensive rat. Erne et al. (1984) also reported increased intracellular calcium in persons with essential hypertension.

Indeed, the hypothesis that much essential hypertension is related to increased intracellular calcium stores was one of the primary motivations behind the use of calcium blockers to treat hypertension, with favourable results in the spontaneously hypertensive rat (McCarron et al., 1985) and in preliminary human clinical experience (Guazzi et al., 1983).

The Sodium-Potassium Pump, Calcium Metabolism and Blood Pressure

Whereas the role of the sodium-potassium pump in regulating intracellular calcium calcium in vascular smooth muscle is still very controversial, there are a number of studies suggesting it may play a part. Clough et al. (1983) found decreased Na/K-ATPase activity in the myocardial tissue of the one-kidney, one-clip hypertensive rat. Ouabain, a potent inhibitor of Na/K-ATPase, has been shown to increase contractibility of smooth muscle tissue and to reduce the effect of extracellular calcium and potassium in relaxing the tissue.

Altered sodium-potassium ATPase activity has been found in persons with essential hypertension (Postonov et al., 1977; Wambach et al., 1979; Garay and Meyer, 1979), and the racial difference in the activity of the sodium-potassium pump is hypothesized to be a component of the higher blood pressure levels found in blacks (Lasker et al., 1983; Weder et al., 1984). Hamlyn et al. (1982) found that plasma from patients with essential hypertension inhibited the activity of canine kidney Na/K-ATPase. Magnesium is a cofactor for the sodium-potassium pump; Whang et al. (1982) found that patients with low serum magnesium levels required a greater amount of antihypertensive medication to achieve acceptable blood pressure levels, and Dyckner and Wester (1983) found that magnesium supplements added to diuretic therapy produced greater decreases in blood pressure in some hypertensive patients.

Lead and Intracellular Calcium Stores

Increases in intracellular calcium concentrations have been noted by investigators of lead. Goldstein (1977) showed that 100 μM lead tripled calcium accumulation in the brain capillaries of rats, and found evidence suggesting that decreased efflux, an attribute of Na/K-ATPase inhibition, was a factor. Kim et al. (1980) found evidence for increased calcium accumulation in brain cells, and Pounds et al. (1982a, b) found clear evidence of increased calcium accumulation in all three compartments of hepatocytes. Interestingly, Pounds and co-workers reported that at low doses, the lead-induced increase in calcium concentration in the three intracellular compartments appeared to be uniform across all three compartments. At high lead levels (50 and 100 μM), two of the smaller compartments saturated out, and the greatest increase was in the deep compartment, thought to include the mitochondria. Rosen (1983) noted a similar increase in intracellular calcium in osteoclasts.

Piccinini et al. (1977) and Favalli et al. (1977) performed several experiments on the tail arteries of normotensive rats. Starting with non-exposed rats, they found that infusion of lead into the medium in doses of 5-15 μM produced a dose-dependent contraction of the arteries, including an increase in the steady-state contraction. In the absence of calcium in the medium there was no effect. In the presence of calcium, the contractile response was independent of the calcium concentration in the medium (in the range of 0.6-2.6 mM) for the control arteries, but for the lead-exposed arteries contractile response increased with calcium concentration as well as with lead concentration (at constant calcium level) in the extracellular medium; this suggests a significant lead-induced effect on the cell's ability to properly regulate calcium levels. When lead was added to the calcium-free medium and then calcium was added, the intitial response to calcium was also exaggerated.

Piccinini et al. (1977) analysed the arterial tissue in the lead-exposed and control arteries and found an increase in intracellular calcium (p 0.01), whereas the fraction of exchangeable calcium in the intracellular media remained the same (and the absolute amount increased).

These results are consistent with the findings of Iannaccone et al. (1981) and Webb et al. (1981), who demonstrated not only that dietary lead increased the blood pressure of normotensive rats *in vivo*, but also that the rats manifested increased contractile response to stimulus (compared with controls). The increased intracellular calcium stores noted above would produce exactly the exaggerated response that was found *in vivo* (Iannaccone et al., 1981) and in the tail arteries *in vitro* after sacrifice (Webb et al., 1981), particularly if the endoplasmic reticulum saturated before the mitochondria began to dominate the calcium increase (Pounds et al., 1982a, b). Moreover, Webb et al. (1981) found that the period of time required to reach half-maximal relaxation following alpha-adrenergic stimulation was significantly longer in the arterial muscle of the lead-exposed rats than in the controls. This fits in well with Piccinini's et al. (1977) observation that *in vitro* treatment with lead increased the half-life of the slow component of radioactive calcium desaturation from the rat smooth muscle. It is also in accord with Webb and Bhalla's (1976) observation that slowed ability to take up calcium in the microsomal fraction, including the endoplasmic reticulum, was associated with the hypertension found in the spontaneously hypertensive rat.

Lead and the Mechanisms of Intracellular Calcium Regulation

There are several plausible mechanisms whereby lead might affect these processes in ways that led to increased blood pressure, and some of these effects have been documented in smooth muscle tissue. First is lead's long-documented interference with the sodium-potassium pump, which can effect both the influx of ionized calcium and its efflux in excitable cells (Pounds, 1984). The inhibition was noted by Hernberg et al. (1967) and others (e.g. Goddard and Robinson, 1976; Raghavan, 1981).

The disturbances in mitochondrial sequestration of calcium noted in the spontaneously hypertensive rat's smooth muscle tissue are also associated with lead. Pounds et al. (1982a) found increased calcium stores in the hepatocyte mitochondria, and lead has been found to decrease the capacity of mitochondria to take up calcium in rat hearts (Parr and Harris, 1976) and rat brains (Goldstein, 1977). Kapoor and van Rossum (1984) reported that lead inhibited the rate of mitochondrial uptake of calcium in renal cortical mitochondria both in tissue and in isolated mitochondria. The finding of both slowed mitochondrial uptake of calcium and increased mitochondrial calcium stores is somewhat surprising, but may indicate a saturation effect. Mitochondrial uptake of calcium is normally very low in smooth muscle tissue at the cytosolic calcium concentrations typical of resting tone, so lead's interference with mitochondrial uptake is more likely to be linked to the increased reactivity and slowed relaxation effects of lead than to its increase in resting tone.

Cyclic-AMP is another important modulator of free cytosolic calcium and smooth muscle reactivity that may be affected by lead. Cyclic-AMP may increase the activity of the sodium pump leading to a decrease in intracellular calcium, stimulate the calcium pump that removes calcium from the cytosol into the endoplasmic reticulum and lead to a phosphorylation of MLCK, reducing its sensitivity to activation by calcium. All of these activities reduce muscle tension (Blaustein, 1977). Goldstein and Ar (1983) demonstrated that lead activated calmodulin in its role of activating phosphodiesterase, the enzyme that converts cAMP to AMP, thereby stopping the activity described above. Thus, by disturbing the balance between calcium and cAMP, lead may increase the reactivity of smooth muscle and slow the return to resting tone in the vascular smooth muscle.

This indicates that the relationship between blood lead level and blood pressure found in the community studies (Beevers et al., 1976; Moreau et al., 1982; Batuman et al., 1983; Pocock et al., 1984; Pirkle et al., 1985; Harlan et al., 1985) not only is supported by the animal studies (Favalli et al., 1977; Piccinini et al., 1977; Perry and Erlanger, 1978; Kopp et al., 1980; Webb et al., 1981; Iannaccone et al., 1981; Victery et al., 1982) but also is consistent with what we know about the ability of lead to alter cellular calcium metabolism.

Moreover, the fact that the cystolic calcium concentration of vascular smooth muscle is normally above that which produces tension suggests that anything that altered that concentration would have an effect on blood pressure, which is consistent with the finding of no threshold for lead's effect on blood pressure in the NHANES II data. It is interesting that the effect of lead on vitamin D metabolism, which is also thought to be caused by increased cellular calcium concentration, is a logarithmic function of blood lead level and has thus far manifested no threshold, although the blood lead levels in the published studies are not as low as in the NHANES II data (3 μg/dL).

Analysis of NHANES II Data

In light of these indications of potential effects of lead on the cardiovascular system, the relationship between blood lead levels and blood pressure has recently been explored (Harlan et al., 1985; Pirkle et al., 1985) using the NHANES II data. The NHANES II is an excellent data base for this analysis because of the care given to accurate measurements and the great range of information on possible confounding factors, and because it is a representative sample of the United States population. As such it avoids the problems of selection bias, healthy worker effect, other occupational exposures and the choice of controls that confound many occupational studies. Harlan et al. (1985) found blood lead level related to blood pressure for males aged 12-74 years after controlling for the traditional variables associated with blood pressure (age, age-squared, body mass index, race) as well as alcohol consumption, socio-economic factors and all nutritional variables suspected of affecting blood pressure. Moreover, this relationship held in each year of the NHANES II sample when analysed separately and for both blacks and whites.

Pirkle et al. (1985) found that blood lead levels were a statistically significant predictor of blood pressure in adult males. This relationship held not only when blood lead level was evaluated in a regression with all known factors that have previously been established as correlated with blood pressure, but also when that relationship subsequently was tested against 87 additional variables representing linear and non-linear functions of every dietary and serological variable in the NHANES II survey. This analysis builds on the Pirkle et al. (1985) study.

Blood Pressure Measurements

Three blood pressure measurements were taken during NHANES II. A seated measurement was taken as soon as the examinee entered. Later, a recumbent measurement was taken. A second seated measurement was taken just before the end of the examination. It is standard medical practice to prefer the second seated measurement, because nervousness on just entering a medical examination centre makes the first seated measurement less stable. All of the results presented are for the second seated measurement. However, almost all of the regressions and robustness tests described were performed on all three measurements and on the average of the first and third seated measurements--all of the conclusions concerning lead's significance held for all eight regressions (four diastolic, four systolic).

Initial Analysis

After replicating the Harlan et al. (1985) results for all adult males, the first goal was to determine if blood lead levels were related significantly to blood pressure in white males 40-59-years-old. This subgroup was chosen for two reasons. Firstly, we wanted to be able to use the Pooling Project's multiple logistic risk factors for cardiovascular disease to determine if the changes in blood pressure associated with lead were of any significance for cardiovascular disease. These factors have been published only for 40-59-

year-olds, and the risk is known to be smaller for younger adults. Secondly, we chose this age group because at lower ages both blood pressure and blood lead level vary with age. This collinearity could artificially mask or enhance the correlation between blood lead level and blood pressure. Between 40 and 59 years of age, however, blood pressure is essentially independent of age. Choosing this subgroup avoids any collinearity problems. We focussed on whites because data relating cardiovascular disease to blood pressure are less extensive for non-whites.

The established correlates of blood pressure are age, sex, race and one of the indices of relative height-to-weight. Body mass index (BMI = weight/height^2) was used in this analysis. By limiting attention to 40- to 50-year-old white males, there was no need to control for race, sex or, to a large degree, age. Although age was only occasionally significant in the stepwise analysis, both age and age-squared were forced into each multiple regression model to be certain any effect of lead was independent of age.

The natural log of blood lead was more normally distributed, was more statistically significant and gave a higher r^2 than untransformed blood lead, blood-lead-squared, blood lead plus blood-lead-squared, the square root of blood lead or blood lead to other fractional powers (0.15, 0.2, 0.3, 0.4). All of the results reported here are for the natural log of blood lead, but regressions using lead on the untransformed scale gave very similar results.

The initial regressions analysed systolic and diastolic blood pressures for white males, 40-59 years old, with a model consisting of age, age-squared, BMI and blood lead level. These regressions were done to determine whether blood lead levels were significantly associated with systolic and diastolic blood pressures after controlling for age, sex, race and BMI, which are well-documented correlates of blood pressure. Lead was statistically significant ($p < 0.01$) for both systolic and diastolic blood pressures in all the regressions (unweighted, weighted and weighted with design effects). The regressions also tested whether this relationship held up when other potentially confounding variables were considered.

Tests of Robustness

The regression models were expanded to incorporate additional variables, with particular attention directed to the stability and significance of the lead coefficient in the presence of nutritional factors and blood biochemistries.

A large set of nutritional and biochemical variables from NHANES II was included in the stepwise regressions. Additional regression analyses considered potential problems of interaction terms. To ensure the robustness of the relationships, further analyses were done to address marginally insignificant variables and non-nutrition variables. Although our analysis focussed on males aged 40-59, additional regressions were also performed considering all males over age 20.

Nutritional and Biochemical Variables

To provide an unusually rigorous test of the independent significance of blood lead level, almost all of the nutritional and biochemical variables in the NHANES II were included in stepwise regressions. In addition, to account for possible curvilinear relationships, squared and natural logarithmic transformations of almost all of these variables were also included. The variables are listed in Table 1. The objective was not to evaluate the possible association of nutritional or biochemical measurements with blood pressure, but rather to estimate conservatively the strength and independence

Table 1.

Variables included in the stepwise regression analysis.

- age*
- age-squared*
- body mass index
- dietary sodium**
- salt-shaker sodium
- dietary sodium salt-shaker sodium
- dietary potassium**
- dietary sodium-potassium ratio
- dietary calcium**
- dietary phosphorus**
- dietary protein**
- dietary fat**
- dietary carbohydrate
- dietary cholesterol**
- dietary saturated fatty acids**
- dietary oleic acid**
- dietary linoleic acid**
- blood lead**
- dietary iron**
- dietary vitamin A**
- dietary vitamin C**
- dietary thiamine**
- dietary riboflavin**
- dietary niacin**
- serum cholesterol**
- serum vitamin C**
- serum iron**
- serum transferrin saturation
- serum zinc**
- serum copper**
- serum albumin**
- hemoglobin**
- red blood cell count
- ethanol consumption/week**
- cigarettes smoked/day
- total dietary grams**
- total dietary calories**
- cigar or pipe smoking

* Forced into each regression to remove any possible age effects on blood pressure.

**The natural log and squared transformation of these variables were also included in the stepwise regression.

of the relationship between blood pressure and blood lead level.

Including these additional 87 variables increases the probability of variables being found to be statistically significant due to chance alone. This complicates the interpretation of nutritional and biochemical factors, but not the interpretation of the lead variable; it only makes it more difficult for lead to maintain its significance.

The general procedure for variable selection was as follows. Firstly, weighted stepwise multiple linear regression was used to determine which variables were significantly related ($p < 0.05$) to blood pressure (using the Stepwise and MAXR options of the Statistical Analysis System (SAS) procedure, STEPWISE). The MAXR procedure was the principal one used; it determines for any given model size (i.e. number of variables) the variables that explain the greatest amount of the variance (i.e. maximize r^2). We chose the largest model with all variables significantly related to blood pressure ($p < 0.05$). The Stepwise option, which uses forward selection with backwards elimination, chose very similar models and also always chose blood lead level. From the 87 nutritional and biochemical variables, the weighted stepwise regression selected five additional variables for diastolic pressure and six additional variables for systolic pressure, using a 5% significance test. These were used as the starting model for the SAS procedure SURREGR, which additionally incorporated the survey design effects. For both systolic and diastolic blood pressures, one variable from the weighted stepwise regression failed to maintain significance at the 5% level after the design effects were incorporated. The final regression results for systolic and diastolic pressures, after accounting for the weighting and design effects, are given in Table 2.

The multiple logistic regressions of the probability of hypertension

Table 2.

Regression of diastolic and systolic blood pressures in white males aged 40-59.

Variable	Coefficient	t-Statistic	Probability
Diastolic			
Age	0.2768	0.17	0.8636
Age^2	-0.0014	0.10	0.9321
Body mass index	1.131	8.55	0.0001
Log (blood lead)	3.954	2.85	0.0080
Dietary potassium	-0.0018	4.92	0.0001
Hemoglobin	1.548	3.90	0.0005
Albumin	3.587	2.50	0.0179
Log (dietary vitamin C)	1.838	4.65	0.0001
Systolic			
Age	1.311	0.57	0.5720
Age^2	-0.0068	0.30	0.7706
Body mass index	1.736	9.42	0.0001
Log (blood lead)	8.436	3.24	0.0028
Albumin	7.088	2.50	0.0178
Log (dietary vitamin C)	2.411	3.84	0.0005
Log (dietary riboflavin)	-5.509	3.07	0.0044
Log (dietary oleic acid)	3.992	2.45	0.0183
Log (serum vitamin C)	-3.472	2.47	0.0184

were also performed using programs for SAS. The procedure LOGIST was used for the stepwise unweighted multiple logistic regression, and the procedure NLIN (non-linear) regression was used for the weighted logistic regression calculations. The selection process again chose the largest significant model that explained the greatest amount of the variance. Calculations of threshold levels for effects were made using the procedure NLIN on segmented regression models, which finds the threshold point that minimizes the sum of the squares of the error terms. The results of the logistic regression on hypertension are shown in Table 3. Note that the logistic regressions included blacks as well as whites, because these regressions were used only to predict the effect of lead on the probability of having hypertension and were not used to estimate the number of cases of cardiovascular disease and deaths. As noted earlier, blacks were not included in the linear regressions because the best available coefficient for predicting cardiovascular risks included insufficient numbers of blacks.

Table 3.

Weighted logistic regression on probability of diastolic blood pressure greater than or equal to 90 mmHg in men aged 40-59.

Variable	Coefficient	t-Statistic	p-Value
Constant	-16.41	10.13	0.0000
Log (blood lead)	0.693	3.96	0.0000
Albumin	0.0873	3.70	0.0001
Body mass index	1.700	9.34	0.0000
Hemoglobin	0.0329	5.25	0.0000
Log (vitamin C)	0.3585	5.98	0.0000
Dietary potassium	-0.00058	7.47	0.0000
Total carbohydrates	0.00246	3.09	0.0010

After including the nutritional variables, the blood analytes and their curvilinear transformations, lead remained significantly associated ($p < 0.01$) with both systolic and diastolic blood pressures. The magnitude of this relationship, adjusted for the other significant variables, is shown graphically in Figures 1 and 2. Furthermore, segmented regression analyses indicated there was no threshold blood lead level in the data.

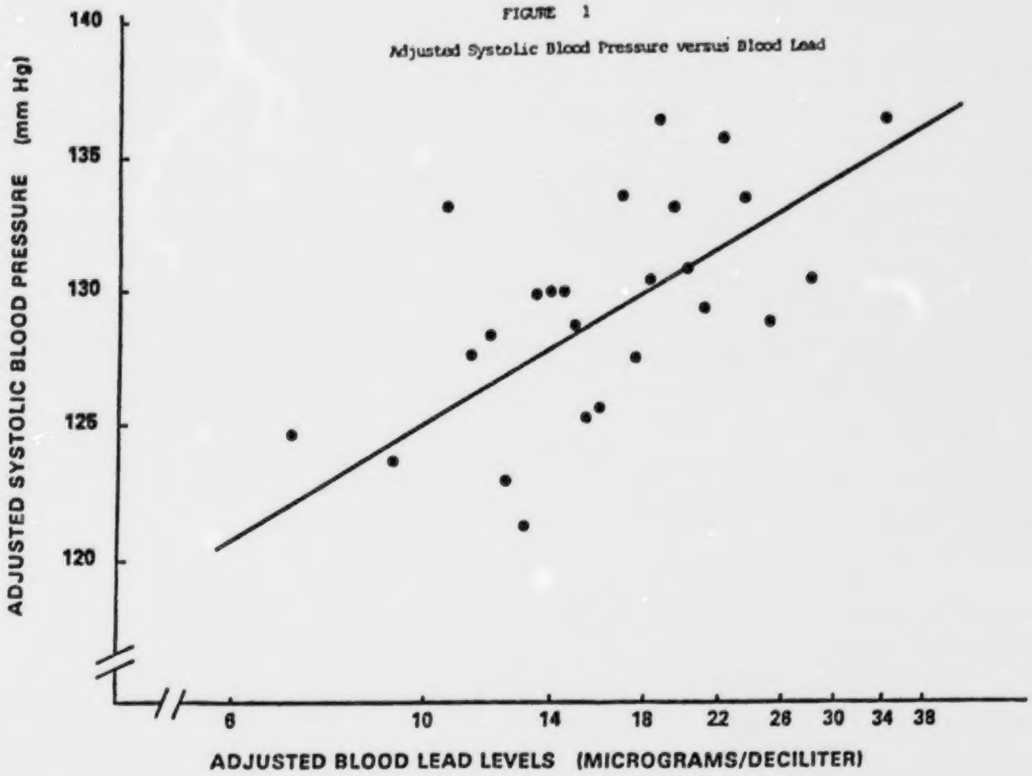

FIGURE 1

Adjusted Systolic Blood Pressure versus Blood Lead

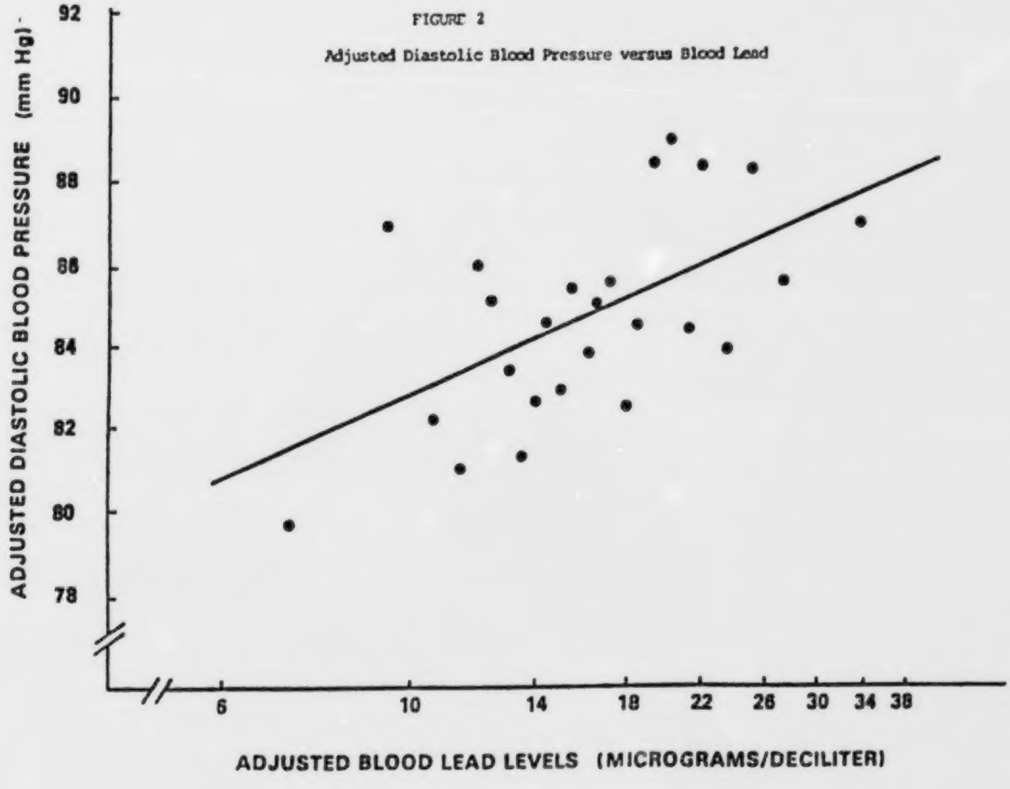

FIGURE 2

Adjusted Diastolic Blood Pressure versus Blood Lead

These segmented 'hockey stick' regressions fit two regression lines to the data. One, below the putative blood lead threshold T, depends on all the variables except lead. The other, for blood lead levels above T, includes lead. An interactive technique is used to find the value of T that minimizes the sum of the squares of the error terms over the full range of both regression lines. In this case, the error in the regression was minimized at a threshold of zero; that is, lead was significantly related to blood pressure at all levels down to zero.

Interaction Terms

In multiple regression analysis, another consideration is the possibility of significant interaction terms. To evaluate this possibility, an additional weighted stepwise regression analysis was done for systolic and diastolic blood pressures. The variables consisted of the linear interaction terms between the final variables in the model (shown in Table 2) and the linear form of all the other variables originally selected for the initial stepwise regression, including their log and square transforms (Table 1). This meant running a stepwise regression with 162 interaction terms added to the final regression models for systolic and diastolic pressures. Using such a large set of variables gave a high probability that some variables would enter at the 5% level by chance. However, the purpose was not to determine if those variables were independently significant but, rather, to test further the significance and independence of the relationship between blood pressure and blood lead level. As expected, several interaction variables entered the systolic and diastolic regressions, but in each regression the lead coefficient varied less than 10% and remained significant ($p < 0.015$).

Marginally Insignificant Variables

Three other analyses were done to ensure that this relationship was robust. Firstly, the original weighted stepwise regression was extended to include variables significant through the 15% level to see if marginally insignificant variables influenced the significance of lead. For both systolic and diastolic pressures, lead remained significant, and there was little change in the magnitude of the coefficient.

Secondly, for diastolic blood pressure, all the variables were included that were significant between the $p = 0.05$ and $p = 0.15$ levels, and every possible combination of those variables was considered. All 255 combinations were added to the variables that were statistically significant, and a regression was performed on each one. The coefficient of the log of blood lead level varied by only ± 10% from the value we obtained when we included only significant variables, and the highest p-value for lead was still less than 0.01.

The last analysis was the most demanding test of the independence of the relationship between blood pressure and blood lead level. Models for diastolic and systolic blood pressures were fitted by weighted stepwise regression to the original model variables (Table 1), excluding lead. This gave all of the other variables and their curvilinear transformations the maximum opportunity to explain variation that could also be explained by lead. After obtaining this new final model without lead, a single regression was run adding the lead variable to the variables of this new final model. For both systolic and diastolic pressures, lead was still statistically significant ($p < 0.016$), and the magnitude of the lead coefficient changed less than 10% from those obtained in the original analysis. The results of all these analyses indicated that the strength and independence of the relationship between blood pressure and blood lead level were remarkably stable.

Because some people have found small amounts of ethanol associated with reduced blood pressure, ethanol was also modelled as a quadratic function of consumption, and with two dummy variables for light and heavy drinking. The stepwise regression was repeated with no change.

Non-nutritional Variables

Pirkle et al. (1985) considered non-nutritional variables that might be associated with blood pressure. In additional runs completed since then, we have added several other variables. The complete set is shown in Table 4. Socio-economic and demographic factors as well as additional medical history variables were included.

Hypertensive medication and low-salt diet were tested, not for inclusion in a final model, as they are essentially indicators of high blood pressure, but rather to see if the response to lead differed in those groups. The coefficient of lead did not change appreciably, and lead interaction terms with the two variables were insignificant.

The other variables in Table 4 were tested in two ways. First, the stepwise regression procedure was repeated with them using all nutritional and serum measurements that were significant at the $p = 0.15$ level. The nutritional factors were limited to those significant at the 0.15 level to give the non-nutritional factors a greater chance to enter the model. Again, lead was selected ($p < 0.005$) and its coefficient changed by less than 10% from the original model that included only age, age-squared and body mass index.

The variables in Table 4 were then added to all of those in Table 1

Table 4.

Non-nutritional variables tested in the stepwise regression.

Demographic Variables

Family income
Poverty index
Region of the country
Season of the year
Degree of urbanization
Residence inside central city
Education level

Hypertensional Variables

Hypertensive medication
Low-salt diet

Other Personal History Variables

Tricep skinfold
Subscapular skinfold
Recreational exercise
Work-related exercise
Recent weight loss
Family history of hypertension
Kidney disease
Serum creatinine

(including their non-linear transforms) and the stepwise process was repeated--with the same results. Finally, the stepwise procedure was rerun using all of the variables in Tables 1 and 4 except lead; lead was then inserted into the model resulting from this procedure. It was still significant ($p < 0.006$), with less than a 10% change in its coefficient. Because the presence of two terms to describe the curvilinear dependence of blood pressure on age might reduce the chances of variables correlated with age achieving significance, age was modelled as a single curvilinear function (sine of age), and the stepwise regression repeated; the results were the same.

In addition, smoking and drinking were forced into the regression, and lead was still significant ($p < 0.01$), with only a 3% change in its coefficient.

Our previous studies have shown that about half of the lead in people in the NHANES II sample came from gasoline. Tetraethyl lead has very little cadmium in it, so confounding with cadmium (which is also suspected of affecting blood pressure) is unlikely. However, we repeated the regression excluding occupationally exposed workers, who may also have cadmium exposure. Lead remained significant ($p < 0.01$), and its coefficient increased somewhat. We also regressed gasoline lead directly on blood pressure, and it was significant.

Although all of these analyses make it clear that collinearity is not a problem in these regressions, variance inflation factors were computed; no significant variable had a variance inflation factor above 1.4. (Variance inflation factors below 4 are considered acceptable in multiple regression analyses.)

To ensure that the significance of lead in the regression was not due to the presence of a few influential observations, influence diagnostic procedures were run. Studentized residuals were plotted for all the observations, and the largest residuals were clustered near the middle of the data, where their influence is slight. Cook's D statistics were also computed for each observation. The highest Cook's D was 0.029, and the second highest was 0.023, both of which are very small. Moreover, of the 10 observations with the largest Cook's D statistics, 6 had positive residuals and 4 had negative residuals, indicating that the most influential observations split almost evenly on which way they would influence the lead regression coefficient.

Because the nutritional variables are often collinear with each other, a second approach was taken to dealing with the nutritional and serological variables. Principal components analysis was done to find the linear combinations of the nutritional and serological factors that explained the greatest amount of their common variation. These principal components were then entered in the stepwise regression to allow those factors to explain a greater amount of the variation in blood pressure before collinearity prevents any more variables from entering. For instance, the first five principal components of the variables in Table 1 explain 50% of their variance. When these were used in the stepwise regression, lead was still significant ($p < 0.01$) and the coefficient had changed by less than 10% from its original value.

Other Age Groups

The 40- to 59-year-old age group represents about one-third of adult males, and is the only one where the confounding of age and blood lead can be eliminated unambiguously. Additional regressions were performed, however, to confirm the Harlan et al. (1985) finding of an effect in all adult males. Tables 1 and 4 contain several variables that Harlan et al. (1985) did not consider in their analysis. Therefore, the stepwise regression analysis was repeated using all of the variables in both tables (plus race) and their square and natural log transforms; all males over the age of 20 were considered. Lead was selected by the regression, $p = 0.0008$ systolic, $p = 0.0039$ diastolic. To ensure that a spurious correlation was not occurring because of an interaction of lead levels with hypertensive medication, or because of persons with kidney diseases and hypertension having elevated blood pressure and blood lead levels due to that kidney disease, and causing a spurious correlation between the two, we reran the regression excluding all persons with hypertension serious enough to require medication. Lead was still significant, $p = 0.0015$ systolic, $p = 0.0018$ diastolic.

To ensure that the relationship was robust to specification changes, the stepwise regression was repeated without lead. Lead was then reinserted, and was significant ($p < 0.01$).

To check whether the relationship must be substantially different for different age groups, dummy variables for the age groups 20-45 and 46-74 years were created, and an interaction term between lead and the dummy for the younger age group was inserted in the regression. Such interaction terms check for differences in the lead/blood pressure relationship without having to subdivide the sample. The interaction term was not significant. Two further tests were done. Firstly, the stepwise regression was repeated separately in both age subgroups, and lead was selected as significant in each one. Secondly, a separate regression was run for the 25 age subgroups 20-49, 21-50 ... 45-74. Lead was significant in each one.

Because lead levels fell during the 4 years of the NHANES II study, two tests were done to ensure that lead was not picking up the effect of a time trend in some other causal variable of blood pressure. We note first that if such a factor were on the two tables listed before, there would be no problem; changes in obesity, exercise, etc. would be attributed to those variables. Fortunately, the lead levels in the United States fell at a much faster rate during the last 2 years of the NHANES study because gasoline lead regulations were changed. If lead were merely correlating with the change in some other factor, that correlation would be different in the last 2 years than in the first 2 years. We therefore tested whether the relationship between blood lead level and blood pressure was different between the first and last halves of the NHANES survey, and it was not (p = 0.75 systolic, p = 0.79 diastolic). As a further test, we inserted a term for time into our regression model, despite not knowing of any time trend in an omitted factor related to blood pressure. Lead was still significant, even with time in the model.

All of the candidate counties in the United States were grouped into 32 strata on the basis of similarity in region, size and socio-economic characteristics, and sample areas were chosen from each strata. To ensure that there was no confounding of lead with location, a variable for each stratum was forced into the regression. Lead was still significant. Then, a variable for each individual stand was included in the stepwise regression. Only a few of the locations were selected as significant, and lead remained significant.

Summary of Blood Lead - Blood Pressure Results

The final models for blood pressure, including all statistically significant variables, are shown in Table 5. The final logistic model for the probability of hypertension is shown in Table 6.

It is noteworthy that the logarithmic form of the dose-response relationship suggests a large initial effect, levelling off at higher blood lead levels. This may explain why only about 60% of the occupational studies (i.e. high-lead exposure studies) have found an effect that was significant at the 95% confidence level, whereas almost all of the studies of lower lead levels have found the relationship to be significant.

The other low-lead exposure studies, the animal data and the robustness of these results suggest that the relationship is causal. Moreover, specific analyses to determine whether there is a lower threshold below which lead has no effect on blood pressure showed that the data were best fit with a threshold of zero.

Table 5.

Regression of diastolic and systolic blood pressures in white males aged 40-59.

Variable	Coefficient	f-Statistic	Probability
Diastolic			
Age	-0.210	0.02	0.8960
Age-squared	0.003	0.04	0.8373
Body mass index	1.082	67.88	0.0000
Blood lead*	4.609	12.19	0.0014
Potassium	-0.002	25.30	0.0000
Hemoglobin	0.151	16.81	0.0003
Albumin	0.354	7.42	0.0104
Dietary vitamin C*	1.886	23.67	0.0000
Family history of hypertension	2.085	4.37	0.0446
Recreational exercise	-1.851	9.48	0.0042
Systolic			
Age	1.142	0.25	0.6226
Age-squared	-0.005	0.05	0.8208
Body mass index	1.710	85.90	0.0000
Blood lead*	8.510	10.54	0.0027
Albumin	0.695	6.09	0.0192
Dietary vitamin C*	2.458	13.78	0.0008
Dietary riboflavin*	-5.101	8.14	0.0075
Dietary oleic acid*	3.650	5.34	0.0275
Serum vitamin C*	3.365	5.81	0.0218
Family history of hypertension	3.683	4.59	0.0399

* Log transform.

Table 6.

Logistic regression on probability of blood pressure greater than or equal to 90 mmHg in men aged 40-59.

Variable	Coefficient	t-Statistic	p-Value
Constant	-15.40	7.0	0.0000
Log (blood lead)	0.793	3.20	0.0014
Albumin	0.650	2.06	0.0399
Body mass index	0.1571	6.57	0.0000
Hemoglobin	0.0265	3.19	0.0015
Log (vitamin C)	0.3593	4.22	0.0000
Dietary potassium	-0.00053	5.33	0.0000
Total carbohydrates	0.00286	2.86	0.0080
Recreational exercise	0.3864	0.128	0.0026

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21. THE NHANES II BLOOD LEAD DATA--USES AND LIMITATIONS

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Introduction

This paper provides my views on statistical analyses of the data from the US Second National Health and Nutrition Examination Survey (NHANES II) study as they relate to human blood lead levels, demographic and locational variables and sampling dates of subjects in the survey. The views expressed are mine, based on my experience in statistics and on various reports, publications and analyses of the NHANES II data, and they do not in any way represent the University of Georgia where I am a Research Professor or the American Statistical Association with which I have been closely associated.

My interest in the NHANES II data began when I was asked by the Ethyl Corporation to review the plan of NHANES II (DHHS, 1981), the presentation of Dr. Vernon Houk (1982) to the US House of Representatives Subcommittee on Environment, Energy and Natural Resources, and the initial Ethyl Corporation (1982) submission to the US Environmental Protection Agency. Since that time, numerous papers and reports have been prepared; some have been published, additional statistical analyses have been done and a report has been issued by the NHANES II Time Trend Analysis Review Group (1983). The various papers and reports purport to demonstrate either that there is a causal relationship (or strong association) between apparently diminishing human blood lead levels and decreasing use of leaded gasoline or that the decrease in human blood lead levels can be largely attributed to other factors, most notably biases in the NHANES II data.

I shall give primary attention to the NHANES II study as the source of data, the Houk statement, the Review Group Report and the latest Ethyl Corporation (1984) submission to EPA. The major points to be made are as follows:

1) The NHANES II study was not designed, nor is it appropriate, for estimation of changes in human blood lead levels over time periods within the extended data collection process, and it contains time-associated biases.

2) An apparent association of two variables, such as blood lead level and gasoline lead use, over time does not establish a causal relationship of one to the other.

3) No good data on leaded gasoline use by sampling location or on individual or group exposure to automobile exhaust are available that may be matched with the NHANES II blood lead data.

4) Alternative explanations of the major portion of the apparent blood lead decrease are possible.

In summary, I can conclude only that the available data known to me are inadequate to either demonstrate or refute a relationship, causal or otherwise, between use of leaded gasoline and human blood lead levels.

NHANES II

NHANES II was designed to be a cross-sectional study of health and nutrition of the United States population, providing estimates of population health and nutrition characteristics valid at the mid-point in time of the survey. A sequence of surveys was planned (DHHS, 1981), and changes in population characteristics from one survey to another were to be considered. Data are available now from NHANES I and NHANES II to estimate change in many health and nutrition characteristics from the mid-point time of the first survey to the corresponding time of the second, but blood lead data were not collected in NHANES I, precluding comparisons on this characteristic. The following quotations (DHHS, 1981) establish the purpose of the surveys:

> In 1969 the Department of Health, Education and Welfare established within NCHS (National Center for Health Statistics) a continuing activity to measure the nutritional status of the U.S. population and to monitor changes in status over time . . . .
>
> The continuing responsibility for measuring and monitoring the nutritional health status of the U.S. population meant that the first assessment survey, NHANES I, would be followed by later assessment surveys. These would permit comparisons with the NHANES I baseline data and thereby allow measurement of changes over time.

A second document (NCHS, 1982) describing NHANES II data makes it clear that biases may exist over time within the survey period, but that valid estimates for the survey mid-point could be calculated:

> Adjusted sampling weights were then computed for 76 age, sex, and race categories in order to inflate the sample in such a manner as to closely reflect the estimated civilian non-institutionalized U.S. population ages 6 months to 74 years at the midpoint of the survey (March 1, 1978).

Mahaffey et al. (1979) wrote a preliminary paper on blood lead analysis before the NHANES II data were available in their entirety. They wrote:

> Normative data obtained from the total sample after the survey has been completed will provide the basis for assessment of relationships between blood Pb and selected health and nutritional indices measured for persons 6 months to 74 years in the general population. Comparisons pf data obtained in NHANES II with other surveys will hopefully augment our understanding . . . . Results also provide a national data base for assessing changes over time to evaluate intervention efforts on a broad scale.

Note the reference to "intervention efforts on a broad scale"; I shall return to this suggestion of intended intervention.

Various sampling biases within the time of data collection of NHANES II have been noted, and doubtless others exist. Such biases effectively prevent periodic estimation of national blood lead levels for time subdivisions of the 1976-80 NHANES II study. Biases included the following:

1) Overrepresentation of the very young (with higher blood lead levels than other age groups), the elderly and low-income individuals in the first 2 years of data collection, with corresponding underrepresentation in the final 2 years.

2) The scheduling of stands (examination locations) was arranged so that the north was avoided in the winter. Possible seasonal effects are confounded with possible north-south effects.

3) Possible exposure to lead in gasoline seems to have decreased over the sequence of examination locations in time, because the percentage of rural residents increased as the data collection progressed with time.

4) Subpopulation representation changed with time, particularly relative to the fraction of the sample made up of blacks and urban dwellers.

Documentation of biases exists. Mahaffey et al. (1979) stated that:

> The preliminary NHANES II data presented in this study overrepresent very young, elderly and low-income individuals and should not be used as normative data.

The description of the Operational Plan of NHANES II (DHHS, 1981) states:

> As in previous cycles of NHES AND NHANES, the scheduling of stands (examination locations) for NHANES II was arranged so that the North was avoided in the winter. This was done because of operational problems that would otherwise have resulted. To the extent that any of the items of data collected by the survey were subject to seasonal variation, this procedure may have resulted in some bias, but since the survey was designed more to measure the prevalence of chronic conditions, seasonal variation was not considered to be a major factor . . . .
>
> Another important consideration in the sequencing of stands was economy in operation. Efforts were made to insure the minimum amount of travel by sequencing examination locations with regard to geographic proximity.

I wish to emphasize possible north-south biases, possible seasonal biases, biases due to the sampling of stands in close proximity in sampling time periods and the reference to measurement of chronic conditions.

Table 3 of the submission of Ethyl Corporation (1982) to EPA, based on NHANES II data, shows a somewhat irregular downward trend for the Percent Residents in Non-Rural (urban) Areas from 78.9% for the first half of 1976 to 43.0% for the first half of 1980. Intuition suggests that residents of higher-population-density areas have higher exposures to lead. ICF Incorporated (1982), reporting under contract for the Office of Policy and Resource Management, Office of Policy Analysis, noted:

> Annest found that blacks and urban dwellers had significantly higher blood lead levels than whites and rural dwellers respectively. Therefore, any correlation between time and the fraction of the sample made up of blacks and urban dwellers, for instance, could account for some of the downward trend in overall mean blood lead levels.

ICF used census data to adjust for certain sample biases related to age, size of community and SMSA districts, and considered whites and blacks separately. Adjustments for other biases noted were not attempted.

The Houk Statement

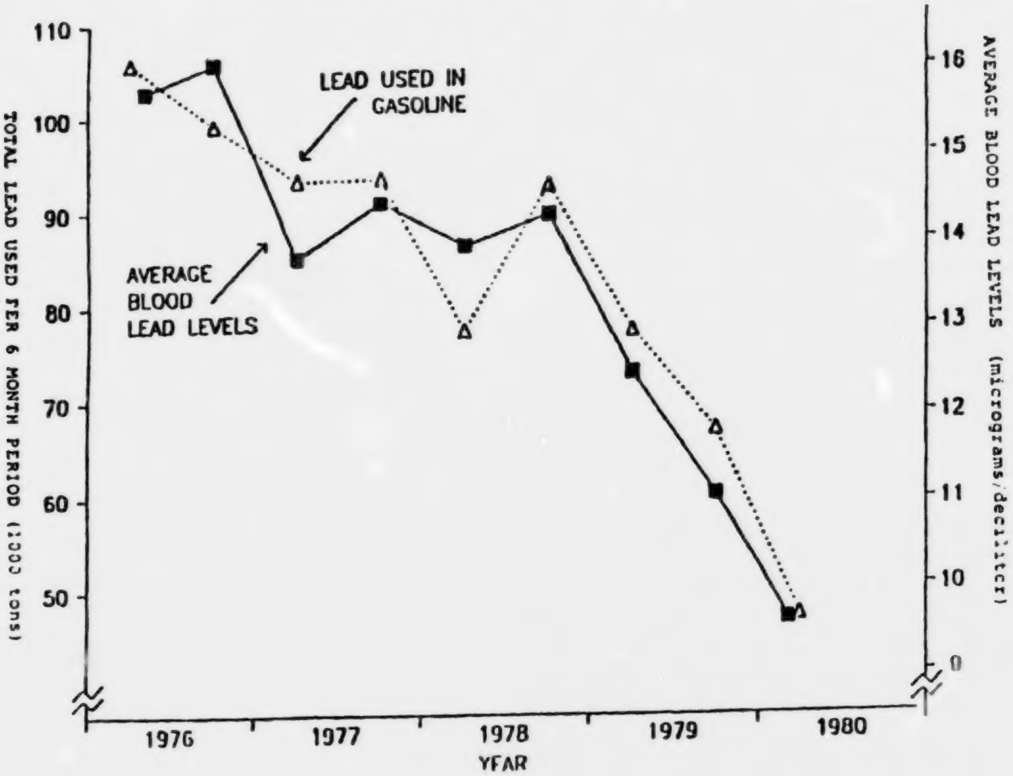
Houk, in his statement to the House Subcommittee, properly summarized knowledge available on human blood lead levels and the adverse effects of lead in the body. In regard to NHANES II, he stated very positively that:

> One significant result of the NHANES II is a decrease over the years of the mean blood lead level from 15.8 µg/dL to 10.0 µg/dL (a 37 percent reduction) (Figure 1). This reduction was real. It was not due to chance, laboratory error, nor sampling of age, sex, urban vs. rural, income levels, or geographic regions. The most significant environmental change during this time was the reduced amount of lead used in the production of gasoline. Figure 2 and Figure 3 show a remarkable association between lead used in gasoline production and the average NHANES II blood lead levels. This clearly demonstrates that as we have removed lead from gasoline, we have also removed lead from ourselves and our children . . . .

> The reduction in the lead being added to our environment has already resulted in a 37 percent reduction in the mean blood lead level and a 50 percent reduction in the amount of lead being added to gasoline. With continued reduction in lead use, we could widen the margin of safety for the lead hazards we have already placed in the environment.

Houk's Figure 2 is indeed dramatic. A copy is shown here as Figure 1. With suitable adjustment of vertical scales, the two trends nearly coincide. Elsewhere in the Houk statement, it is noted that the correlation between gasoline lead use and blood lead level is 0.95. Is Houk correct in his very definite conclusions? Almost certainly the answer is no, at least as to a degree.

Figure 1 NHANES II Data: Blood Lead versus Gasoline Lead (Feb. 1976 - Feb. 1980)



I have discussed biases in the NHANES II data, biases directly associated with the demographic and locational variables disclaimed by Houk. In the second last section of this statement, we shall show how these variables account for most of the apparent decreases in human blood lead levels plotted in Houk's Figure 2.

Houk's statement is apparently based on a preliminary version of the paper by Annest et al. (1983) published later in the New England Journal of Medicine. It is interesting that Annest has now forgotten (see earlier quotation) that the purpose of NHANES II was to provide normative data for comparison with future surveys. We see also that NHANES II is now being used to consider dynamic population changes for relatively short time periods rather than to "measure the prevalence of chronic conditions".

Let us look at Houk's Figure 2, shown here as Figure 1. Suppose that, in leaded gasoline, there is, or could be added, an inert, harmless ingredient, in amounts proportional to the added lead components. A plot, with scale suitably adjusted, of use of this harmless ingredient could be made to correspond exactly with that for 'total lead used'. Would we claim that this ingredient caused elevated human blood lead levels? Many other variables declined from 1976 to 1980, perhaps average weight of new automobiles sold, the rate of inflation, some stocks on the New York Stock Exchange, the use of lead in paint or use of lead in solder in food containers. Are these variables, or some of them, causing elevated human blood lead levels? If we examine only the blood lead levels in Figure 1, apparently decreasing with time, we might conclude that the human body is rapidly developing resistance to lead exposure of various kinds. Probably none of my readers will prefer one of my alternative explanations to the claimed causal effect of lead used in gasoline on blood lead level. Why? Surely only because of subjective intuition--the data of NHANES II and the arguments used would equally well support an argument for any other variable with a nearly coincident time trend.

Yule, in his 1926 presidential address to the Royal Statistical Society in Britain, discussed time-induced correlation and noted a correlation of 0.95 between the standardized mortality per 1000 persons in England and Wales and the proportion of Church of England marriages, from 1866 to 1911. He went on to assert that "the correlation is simply sheer nonsense", although rationalization is possible. Greenwood commented:

> The practical problem involved in the paper (of Yule) was of particular importance to all concerned with medical statistics, because of the tendency to infer conclusions from the apparent concurrence of time series . . . .

Current medical research workers are still enthusiasts, and the tendency to infer such conclusions persists. To examine data, collected at expense for other purposes, to note associations among variables to seek possible direction for future fruitful research is desirable, perhaps mandatory; to attempt to use such associations as a basis for government intervention is indefensible, in my opinion.

The NHANES II Time Trend Review Group

By February 1983, and following the Houk presentation, a substantial array of reports, publications, letters and statistical analyses had been completed, showing that use of NHANES II data to relate use of lead in gasoline and blood lead levels was substantially more complex than suggested by Houk. Efforts centred on quality of data, adjustments for bias and regression modelling to control for demographic variables and changes in them as the NHANES II sampling progressed. In the indicated month, the NHANES II Time Trend Review Group was appointed to evaluate statistical analyses available; the report of the Review Group was issued on June 15, 1983.

Let me summarize as briefly as possible the findings of the Review Group, and comment as appropriate. The Review Group reviewed sources of bias in the NHANES II study. It did not perceive difficulties in quality control related to blood sample collection or blood lead measurement and was concerned with non-response biases (39.3% of sampled persons had missing lead values), but decided that it was unlikely that possible biases from non-response could account for the downward blood lead trend. In regard to the survey design, it was reported:

> Although a cross-sectional design such as the one utilised in NHANES II certainly is not optimal for investigating time trends, one can consider making adjustments within the sample for the effects of relevant covariables such as age, sex, race, residence, and income, if the distributions of these covariables are not highly confounded with time . . . . There has been a striking decrease in the number of bloods taken from white urbanites across the four years . . . . Further examination of the CDC tabulation (App. D2, item 20) indicates sparse information on blacks . . . . The Review Group finds that despite obvious trends over time for such characteristics as degree of urbanization and the proportion of children aged 0.5 to 5 years, the sample size is distributed across the grid of covariable levels sufficiently to permit reasonable adjustments.

On the matter of weights (to make adjustments for disproportionate sampling of demographic groupings), the Review Group considered unweighted averages, averages using basic weights and averages using final lead subsampling weights. The Review Group found that each weighting scheme for each of the 64 stands gave quite consistent blood lead levels and concluded that, with the similarities between the weighted and unweighted analyses, data analysis is not dependent on the particular choice of weights. The summary conclusion was:

> Changes can be estimated for the U.S. population and for major population subgroups, as specified in the previous subsection. Because of sampling error, laboratory measurement error, a high nonresponse

> rate, and the need to adjust for time-related imbalance in the survey design, such estimated changes should be interpreted with caution.

Caution, indeed! Any statistical model or associated analysis involves implicit assumptions, stated or otherwise. Questions arise on the adequacy of the model, the representativeness of the sample, the presence of factors influencing results but not recognized, and so on. For a given sampling time period, it is clear that stands (locations) used cannot possibly represent more than local geographical areas and not the whole United States. To produce blood lead level averages, however weighted to adjust for demographic imbalances for the United States population for selected time periods, it is necessary to assume absence of location effects. Furthermore, if differences among demographic groups differ by location, weighting for imbalances may only accentuate such locational effects. I do not believe that means exist for adjustment for location biases based on tenable assumptions. The use of locational effects in the model of the next section confirms their importance.

In discussing the association of blood lead and gasoline lead changes, the Review Group made it clear that two approaches are possible: (i) an assumption on external authority of a causal relationship, or (ii) a neutral position that leaves the interpreter of analyses to assess the importance of suggested explanations.

Various regression modelling issues were discussed with focus on two that had an impact on final results: (i) measurement on gasoline lead use, and (ii) inclusion of time as a control variable. Most analyses seem to assume an immediate response in blood lead level to leaded gasoline use, although there has been at least one limited attempt to use lagged gasoline lead variables. I am not qualified to speak on the physiology of absorption of lead in the blood, but it does seem relevant to interpretation of NHANES II data analyses.

Ethyl Corporation's (1982) first submission was applauded for its attempt to represent two kinds of lead exposure through the use of population density and a more local measure of lead usage per square mile for the sample locations. There were, however, anomalies in the latter measure that caused the Review Group to reject analyses based on it. In revised Ethyl Corporation analyses discussed in the next section, national gas lead use data from the quarterly EPA Lead Additive Reports were used as less sensitive to criticism, but also less representative of local exposure.

The Review Group report concluded with:

> The CDC and ICF/EPA analyses relating the NHANES II blood-lead data to a national measure of the amount of lead used in gasoline indicate that the drop in average blood-lead levels can be explained, in large part, by the concurrent drop in gasoline lead. This by no means confirms the hypothesis that the blood lead decrease was caused by the decrease in gasoline lead but, in the absence of scientifically plausible alternatives, that hypothesis must receive serious consideration.

I agree with this summary in that national lead use in gasoline can explain the apparent drop in average blood lead levels, even if national lead use in gasoline largely acts only as a surrogate for time. I can also agree that serious consideration must be given to the causal hypothesis. This consideration must be through further research, not acceptance of the hypothesis.

The Revised Ethyl Corporation Analysis

Following the comments of the Review Group, Ethyl Corporation (1984) submitted a new analysis of the association of lead used in gasoline and blood lead based on the data of NHANES II. To avoid further criticism, the lead use data of the EPA Lead Additive Reports were used. A single model regression analysis was used on a per-individual basis which implies use of unweighted averages for quarterly population estimates. However, it could be argued also that the analysis simply considers individual blood lead levels as they depend on the personal characteristics and locations of individuals. Time of sampling is not included as an independent variable. The analysis shows that blood lead levels may be explained on the basis of personal and locational characteristics of the respondents alone, and, quite contrary to Houk's statement, it has not been demonstrated that human blood lead changes are caused by corresponding changes in the use of leaded gasoline.

The set of personal characteristics of individuals in the sample has now been enlarged and includes urban versus rural residence classifications, age, sex, race, family income, working or not, residence air-conditioned or not, alcohol consumption, smoking characteristics, individual's opinion of health, amount of individual non-occupational physical activity and occupation subject to lead exposure or not. Information on all of these variables came from the NHANES II data tapes, some of which were not available to Ethyl Corporation earlier. Only about 330 individuals were identified as being associated with high-lead occupational exposure.

Sixty-two locations or sampling sites were used as data were not available on gasoline lead use for the first two sampling sites in the first quarter of NHANES II sampling.

The simple regression model may be written as:

$$Y_\alpha = \beta_o + \Sigma\beta_i X_{i\alpha} + \Sigma\lambda_j Z_{j\alpha} + \Gamma W_\alpha$$

where, for $\alpha = 1, \ldots, N$, the sample size, Y_α is blood lead, $X_{i\alpha}$ is personal characteristics, $Z_{j\alpha}$ specifies sampling site, and W_α specifies gasoline lead use for the quarter in which the individual is sampled. The Greek letters β,

λ and r in the model are regression coefficients to be estimated from the data.

The regression analysis is summarized in the Ethyl Corporation submission, and further details are on record there (Table 1). The analysis shown based on the Type II SS column shows that 24% of the total variation in blood lead is explained by the personal characteristics, an additional 9.6% explained as the additional effect of locations or sites, and a negligible amount explained by leaded gasoline use, the latter not approaching statistical significance, even with the large number of degrees of freedom available for estimation of the error mean square.

I have plotted unweighted average blood lead levels by quarter after adjustment for personal characteristics and location (Figure 2). Compare Houk's Figure 2 (Figure 1) with this new figure! I have noted that the effect of Houk's figure was dramatic. I leave you to your own conclusion after seeing Figure 2.

A few technical comments on our model are necessary. It is about as simple as possible. The inclusion of interaction terms (cross-product terms in the variables) might improve the estimation and further reduce unexplained variation. The inclusion of squared terms might allow for some curvature in response over time. The inclusion of additional terms is not necessary to make my point.

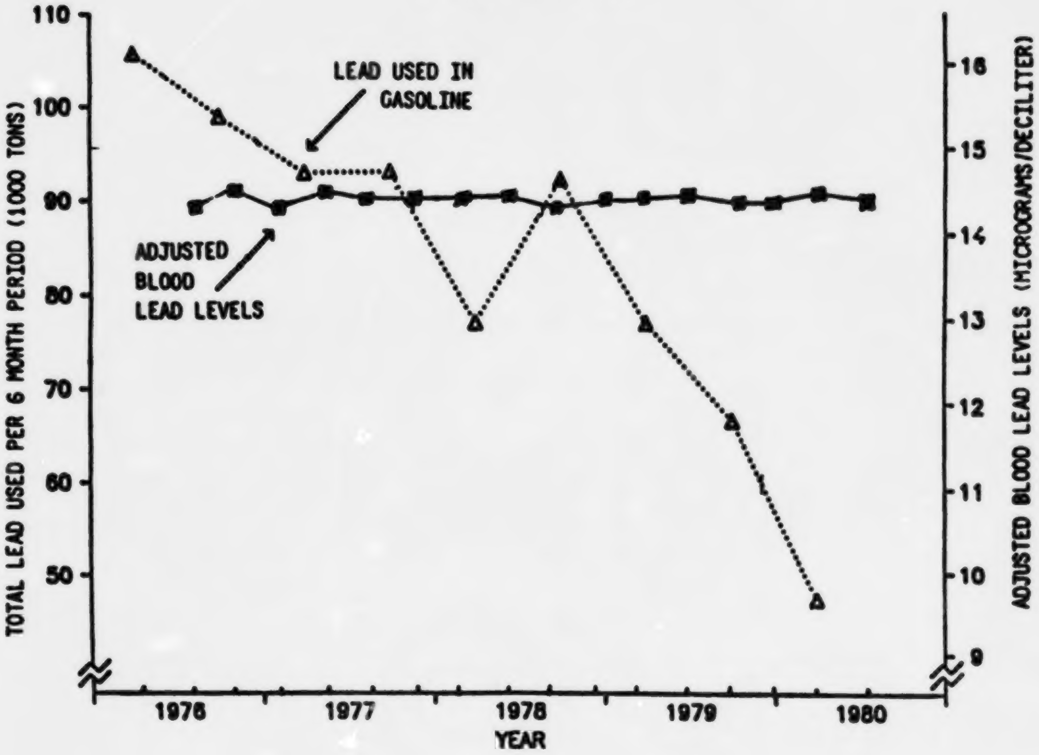
In NHANES II, sampling sites were randomly selected and then individuals were chosen within the sampling location. One might argue that variation among individuals within sampling sites, after adjustment for personal characteristics, yields a sampling error, whereas variation among adjusted location averages provides the proper basis for assessing the effects of

Table 1.

Augmented basic regression model summary.

Source	DF	Type I SS	Mean Square	F Value	PR > F	Type III SS	Mean Square	F Value	PR > F
Population of Home Site	3	1374.513	4580.8	170.66	0.0001	1066.693	355.6	13.25	0.0001
Age	2	12618.611	6309.3	235.05	0.0001	4778.324	2389.2	89.01	0.0001
Sex	1	27901.018	27901.0	1039.45	0.0001	14243.729	14243.7	530.65	0.0001
Race	1	10717.931	10717.9	399.29	0.0001	7655.263	7655.3	285.20	0.0001
Family Income	2	4546.079	2273.0	84.68	0.0001	3537.187	1768.6	65.89	0.0001
Working	1	5788.812	5788.8	215.66	0.0001	1962.760	1962.8	73.12	0.0001
Air-Conditioned Home	1	1064.760	1064.8	39.67	0.0001	590.956	591.0	22.02	0.0001
Drink Beer	1	3551.261	3551.3	132.30	0.0001	1377.849	1377.9	51.33	0.0001
Drink Wine	4	1292.731	323.2	12.04	0.0001	1191.903	490.7	11.10	0.0001
Health Level	5	315.062	63.0	2.35	0.0383	501.316	100.3	3.74	0.0024
Cigarette Smoker	2	6075.424	3037.7	113.17	0.0001	5197.411	2598.7	96.81	0.0001
Cigar Smoker	2	423.621	211.8	7.89	0.0004	416.467	208.2	7.76	0.0004
Exercise Level	2	348.722	174.4	6.50	0.0015	332.208	166.1	6.19	0.0021
Occupational Lead Exposure	1	2644.260	2644.3	98.51	0.0001	2649.150	2649.2	98.69	0.0001
Location	61	36232.355	594.0	22.13	0.0001	16818.990	275.7	10.27	0.0001
Gasoline Lead Usage	1	14.249	14.3	0.53	0.4663	14.249	14.3	0.53	0.4663
MODEL	90	127277.417	1414.2						
Error	9366	251403.589	26.8						

FIGURE 2. **LEAD USED IN GASOLINE PRODUCTION AND ADJUSTED NHANES II BLOOD LEAD LEVELS (FEB. 1976 - FEB. 1980)**



changes in gasoline lead use. Even if this is a more appropriate model (assuming location effects as random rather than fixed), such analysis will only inflate the error mean square in testing for the effect of leaded gasoline use and be more conservative than the Ethyl Corporation approach. The recent DuPont (1984) analysis uses this approach.

Critics of the new Ethyl Corporation (1984) analysis may argue that variables used in the model are acting as surrogates for time. Indeed, we have been accused of throwing the baby out with the bath water. This may be so. The bath water is very murky; the baby may not have existed. None of the variables used is unreasonable; the differences in lead exposure may certainly exist for different locations of the same general description and by season, and differences in lead exposure may certainly exist for different personal situations. If variables used in the model act as surrogates for time, the only possible conclusion is that the serious time biases of NHANES II confound effects and render that study useless for relating blood lead level and gasoline lead use.

Have we demonstrated that gasoline lead use does not affect blood lead level? No. We have demonstrated that other reasonable variables can account for the decline in blood lead level ascribed to gasoline lead use decline.

Summary

I believe that I have documented or demonstrated the four major claims of my introduction. I believe that the new Ethyl Corporation analysis and others show that reasonable alternative explanations for the apparent decline in blood lead levels over the 4 years of NHANES II exist, and that the quick implication that the decline in use of leaded gasoline is the causal variable or even a strongly associated variable is no longer tenable on the basis of evidence from NHANES.

The US Environmental Protection Agency has issued various news releases suggesting in detail the benefits and costs associated with the further reduction or elimination of the use of lead in gasoline. These pronouncements assume extrapolation relative to further reduction in blood lead level to be expected from intended further reduction in gasoline lead use. Even if one were to accept the association presented by Houk, such extrapolation involves the assumption that the downward trend in blood lead level will continue. Such an assumption cannot be fully tenable, perhaps not tenable at all, because one would expect that there is some threshold or background level for human blood lead from sources other than gasoline lead use.

These statements neither exonerate nor indict gasoline lead use as affecting blood lead level. Only further research can settle the matter--research that will be difficult to design and that must be of high quality.

Great care would be needed to plan and conduct research to investigate properly the effect of gasoline lead use on human blood lead level. Such research is needed if intervention, if required, is to have a sound scientific basis. One would expect a research plan that sampled individuals at selected locations, monitored blood lead levels of the same sampled individuals at several time points, provided some reasonable measure of individual or local gasoline lead exposure and had a model accounting for these and other expected sources of variations. Such a plan would properly adjust for the effects of location, as was attempted in the Ethyl Corporation analysis discussed.

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22. LEAD AND BLOOD PRESSURE

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In early 1985 two papers reported on a relationship between blood pressure and blood lead levels found in the National Health and Nutrition Examination Survey (NHANES) (Harlan et al., 1985; Pirkle et al., 1985). This association was present at lead levels generally considered safe. These findings have spurred considerable controversy concerning the effects of lead on blood pressure, and the blood levels at which this effect might be seen. The demonstration of a causal relationship between lead and blood pressure, especially at low blood levels, might have important implications for national policy concerning acceptable levels of environmental lead contamination from various sources. The goal of this paper is therefore to review the literature on this topic, keeping in mind some of the features which imply causality. These include the establishment of the strength of the association, consistency between different studies, a dose-response relationship, evidence supporting the biological plausibility of the association and, finally, confirmatory results of controlled experiments. We will first review the animal literature and then the human studies.

Animal Studies

Two types of animal studies are relevant to a discussion of the potential relationship between blood lead level and blood pressure. Firstly, there are those in which lead is fed to animals and blood pressure subsequently measured. Secondly, there are both in vivo and _in vitro_ studies which attempt to demonstrate a mechanism by which lead could raise blood pressure.

Studies of Variation in Blood Pressure with Lead Intake

In vivo studies measuring blood pressure in lead-exposed rats have been made by three groups of investigators, two of which reported blood lead levels. Victery et al. (1982) added either sodium acetate (control), 100 ppm lead or 500 ppm lead to the drinking water of 15 pregnant rats. Exposure was continued throughout the nursing period and the subsequent 6-month study period, during which the blood pressure of the 51 male offspring was measured monthly. At 3½ months of age the male rats drinking 100 ppm lead showed a significant increase in blood pressure which persisted for the rest of the experiment (average difference 19 mmHg), and was again statistically significant at 5 and 6 months. At 4 and 5 months there were no significant differences among the female offspring between controls and the animals fed 100 ppm lead. Plasma renin activity was lower in the 100 ppm group but not in the 500 ppm group. Plasma creatinine was normal and there were no renal histological changes. The animals drinking 500 ppm lead tended to have lower blood pressures than the controls throughout the experiment, but at no time was the difference statistically significant. The 500 ppm lead group, however, showed other evidence of toxicity such as decreased weight gain. Mean blood levels in the 100 ppm lead group were 40.4 μg/dL and in the 500 ppm group 70.8 μg/dL.

It should be noted that this study used relatively large doses of lead, making it difficult to reach any conclusions about low-level lead effects. It is of interest also that there was no hypertensive effect of lead in the female rats. This discrepancy between males and females is seen in other studies discussed below, including NHANES. The failure of 500 ppm to produce a hypertensive effect is not surprising, as the animals lost weight and showed other evidence of toxicity. Hypertension often tends to disappear in toxic or sick animals and humans.

Perry and Erlanger (1978) and Perry et al. (1978, 1979) investigated the effects of much lower levels of dietary lead on blood pressure in rats. They examined the effects of different metals on the pressor effects of cadmium and found that, unlike selenium, copper and zinc, lead augmented the pressor effects of this metal. By itself, lead produces an effect comparable with that produced by cadmium, and when rats were fed both lead and cadmium the effects on blood pressure were at least additive.

In another study, Perry (1985) added lead acetate to the drinking water of female Long-Evans rats from a single source in concentrations of either 0, 0.01, 0.1, 1 or 5 ppm, starting at weaning. There was no effect on blood pressure in rats fed 0.01 ppm. At 0.1-5 ppm, however, hypertension developed after several months, the effect being nearly maximal at 0.1 ppm. The average increase in systolic blood pressure was 15-25 mmHg. At 0.1 ppm there was a trend towards an increasing hypertension with age (from 3 months to 9 months). With larger exposures, however, the major effect occurred early and waned with time. Discontinuing lead exposure did not reverse the increase in blood pressure. Although the addition of 0.35 ppm selenium corrected the hypertension in cadmium-fed rats, it had little effect in the rats exposed to cadmium plus lead.

The hypertensive effects of lead shown by Perry (1985) were found at 0.1-1% of the dosage of lead used to produce hypertension in Victery et al.'s (1982) experiments described above. However, Perry did not report any blood lead levels, and it is difficult to know how these low doses translate into blood levels. Nevertheless, the effects seen at these low intake levels may be more relevant to the present situation in humans, but comparison will have to await future publication of blood lead levels.

Iannaccone et al. (1981) also measured systolic blood pressure in rats at blood lead levels of 38 μg/dL and compared them with controls. They, too, found an increased systolic blood pressure in the lead-exposed animals.

Animal Studies of a Mechanism for Lead's Effects on Blood Pressure

Animal studies which have looked for a potential mechanism for lead-induced hypertension have focussed on two hypotheses: (i) lead increases intracellular calcium in vascular smooth muscle, leading to increased arteriolar tone; and (ii) lead alters renin metabolism.

The Effect of Lead on Calcium Metabolism. The role of intracellular calcium in stimulating the contractile mechanisms of vascular smooth muscle is well known. Stimulation of excitation contraction coupling by increased intracellular calcium leads to both increased smooth muscle tone and increased reactivity of the vascular tree to alpha-adrenergic receptor activation. Evidence that lead increases intracellular calcium comes from studies by Webb et al. (1981) and by Piccinini et al. (1977). Piccinini et al. (1977) placed tail arteries from rats not previously exposed to lead in a supporting medium into which they infused lead in concentrations from 103 to 309 μg/dL. They found a dose-dependent contraction of the arterial muscle, restricting the flow of fluid through the artery. Lead also induced an increase in tissue calcium with a corresponding increase in intracellular free calcium. The administration of calcium brought about similar contractions only at 100 times greater concentration. These results suggest that lead-induced increases in vascular smooth muscle tone result from calcium accumulation and an increase of the intracellular exchangeable calcium available to contractile mechanisms. The sites of action may therefore be intracellular calcium stores and the cell membrane.

Webb et al. (1981) studied arterial strips equilibrated in saline solution containing either lead acetate or sodium acetate, in addition to strips of tail arteries from the rats chronically fed lead by Victery et al. (1982). The arterial strips from lead-treated rats contracted more vigorously in response to alpha-adrenergic agonists, but there was no difference between groups in the maximum force generated in response to high potassium concentrations. Adrenergic stimulation and potassium depend on two different mechanisms to produce contractions, in that the contractile response to potassium is the result of an influx of extracellular calcium into the cell, whereas the adrenergically mediated contractile response results from an initial release of intracellularly bound calcium followed by an increased cellular membrane permeability to calcium. These results, therefore, suggest that the increased reactivity of arterial muscle in lead-exposed rats is related to an increase in the amount of intracellular calcium available for the activation of contraction.

Further indirect support of this concept comes from Kopp et al.'s (1980) study of cardiac metabolic changes after low-level lead exposure, which showed a somewhat unusual depression of the His Purkinje system excitability by lead. This suggests subcellular cation-selective binding or competitive mechanisms with essential metals.

Effect of Lead on Renin Metabolism. Evidence that lead alters renin metabolism has been found only at considerably higher doses. Fleischer et al.

(1980) added 500 ppm lead acetate to the drinking water of male rats and showed significant alterations in renin metabolism, namely increased plasma renin activity, a blunted response to sodium deprivation and reduced ability to decrease sodium excretion in response to dietary changes. Blood lead levels were not measured but were estimated to be 30 µg/dL from the erythrocyte concentrations and the hematocrit. This value is surprisingly low, considering that Webb et al.'s (1981) rats fed 500 ppm had blood lead levels of 70 µg/dL.

Further indirect support for a renal mechanism of lead in hypertension is provided by Goyer et al. (1970), who showed that the most sensitive indicator of lead poisoning is the presence of intranuclear inclusions which have a characteristic ultrastructural appearance. Most of the lead retained by the rat kidney in lead poisoning is located within these inclusion bodies, with other soft tissues having only a small fraction of the kidney lead concentration. These results were also obtained with high lead concentrations, the rats having been fed 80-10,000 ppm lead prior to being killed at 10 weeks of age.

Summary of the Animal Studies

In summary, (i) three groups of investigators have shown increased systolic blood pressure in rats fed lead acetate in varying concentrations; (ii) several investigators have shown that lead induces changes in smooth muscle by interfering with calcium metabolism; and (iii) high doses of lead have been shown to alter renin metabolism (>100 ppm fed in water).

One feature of the animal studies is the lack of a clear relationship between the dose of lead fed to the animals and the subsequent blood lead levels. It would appear, however, that exposure to lead can produce hypertension in rats, and there is evidence for a plausible physiological basis for this effect.

Human Studies

Investigations of the relationship between blood pressure and blood lead level in humans consist of studies of populations in which lead levels are extremely high, such as lead workers, and ecological and epidemiological studies relating blood pressure to the blood lead levels seen in the general population. As well there have been several studies looking at blood pressure in lead-exposed children.

Studies in Populations with High Lead Levels and Prolonged Exposure

Mortality Studies of Lead Workers. Studies comparing the mortality experience of lead workers with that of the general population suffer from several limitations, such as the inability to control for confounding variables, the fact that workers are generally a disproportionately healthy part of the population (the 'healthy worker effect') and frequently a lack of data on individual exposures. In addition, mortality studies are an insensitive method of studying a condition which is not uniformly fatal, such as hypertension. Hypertension is, however, frequently associated with cardiovascular disease, and is the most common cause of renal failure and cerebral hemorrhage. It is therefore noteworthy that several investigators in different countries have consistently noted increased mortality from chronic nephritis and cerebrovascular disease in lead workers, thus providing indirect evidence of a link between toxic levels of lead and hypertension.

Dingwall-Fordyce and Lane (1963) were the first to report an excess mortality from cerebrovascular disease in employees of lead industries. They studied the causes of death of 184 of 425 men who became pensioners from lead and battery factories between 1926 and 1960, and compared their death rates with the expected death rates of the entire male population of England and Wales. They found a significant excess of deaths from all causes among those pensioners who had experienced the greatest lead exposures, as well as a significant excess of deaths from 'cerebral hemorrhages, cerebral thrombosis and cerebral arteriosclerosis' in that same group (observed 24, expected 9.3).

Recently, Malcolm and Barnett (1982) updated this study, studying the causes of death of 754 of 1898 pensioners from 1925 to 1976. In addition to an excess of death from cerebrovascular causes (observed 43, expected 33.7), they found an increased mortality from nephritis and nephrosis during the years 1935-58 in both the middle- and high-exposure groups. There were, however, no excess deaths from cerebrovascular accidents in the middle-exposure groups despite blood lead levels that are in the toxic range by today's standards. There were no excess deaths from hypertension in any of the groups.

Davies (1984) reported similar findings in a group of 57 chromate pigment workers who suffered clinical lead poisoning from 1930 to 1945. Long-term follow-up (to 1981) showed an excess mortality from nephritis (observed 3, expected 0.24) and from cerebrovascular disease (observed 9, expected 2.2). Again, there were no deaths attributed directly to hypertensive disease.

Similar patterns emerge from studies of smelter workers in Australia and the United States. McMichael and Johnson (1982) examined the causes of death of 140 Australian smelter workers who had been diagnosed as having lead poisoning between 1928 and 1959. Standardized proportional mortality rates, comparing causes of death between lead-poisoned workers and other workers, and comparing workers with the general Australian population, showed excess deaths from chronic renal disease and cerebral hemorrhage among the lead-poisoned workers.

In the United States, Selevan et al. (1985) compared the mortality experience of a cohort of 1987 males employed between 1940 and 1965 at a lead smelter in Idaho with that of the entire US white male population. Again, excess mortality was noted from chronic renal disease (standardized mortality ratio (SMR) = 1.92, confidence intervals 0.88-3.64), with risk increasing with duration of employment (after 20 years of employment SMR = 3.92, CI = 1.07-10.04).

The only mortality study among lead workers which has noted excess mortality from hypertensive heart disease and other hypertensive disease is that of Cooper (1984). He compared the mortality experience of 4519 male employees of 10 battery plants and 2300 employees of 6 lead production plants with the expected mortality rates based on the general US male population. He found excess mortality from all causes with significantly elevated mortality from hypertensive heart disease, other hypertensive disease and chronic nephritis.

None of the above authors used a life table approach to mortality analysis. Thus 'excess deaths from all causes' is dependent upon the point in time selected to look at the data. In the case of premature mortality, an early look at the data may show an excess of deaths, whereas in a later study the general population may have had time to 'catch up'. These studies have not, therefore, addressed the issue of excess premature mortality among lead workers. Nonetheless, such studies can detect excess deaths resulting from particular causes, and the consistent finding of excess mortality from chronic nephritis and cerebrovascular disease suggests that this is likely to be a true result. We can conclude that renal disease and stroke are complications of lead poisoning and of the very high exposures to lead seen in the lead industry in the first half of this century. With present-day exposures, such complications are less likely to be found.

Morbidity Studies.

a) Lead Workers

In order to test the hypothesis that the excess mortality from chronic nephritis and cerebral hemorrhage in lead workers is related to hypertension, one would like to examine the blood pressures of large groups of lead workers. Unfortunately, such large studies have not been made. Cramer and Dahlberg (1966) failed to show an association between hypertension and lead exposure in a group of 364 battery factory workers. In that group 46 workers were found to have diastolic hypertension: the expected number was 51. On the basis of urinary coproporphyrin tests, employees over 55 years of age were divided into a 'lead-affected' group (n = 141) and an unaffected group (n = 132). There was no difference in the prevalence of hypertension between these two groups.

More recently, Kirby and Gyntelberg (1985) reported a study of cardiovascular risk factors in lead smelter employees. They compared 95 employees with over 9 years of lead exposure with controls matched with respect to sex, age, occupational status and duration of employment, and who had had blood lead levels measured as part of a health survey. Mean blood lead levels in the employees were 51 µg/dL, and in the controls 11 µg/dL. There were differences in diastolic blood pressure between the two groups (means: sitting--employees 86 mmHg, controls 82 mmHg, $p = 0.04$; supine--employees 83 mmHg, controls 78 mmHg, p = 0.005), but no significant differences in systolic pressures.

Neither of these studies provides the necessary data on blood pressures and lead levels in large enough samples of employees to be able to draw conclusions about any potential association between lead and blood pressure. One other study on men with occupational lead exposure again does not directly address the issue, but suggests a possible renal mechanism for hypertension at high lead levels. Boscolo et al. (1981) measured urinary kallikrein activity in 22 lead-exposed men who were hospitalized for diagnostic purposes, and in two groups of age-matched healthy controls. Eight of the lead workers had a diagnosis of hypertension and/or nephropathy (mean age 52, mean duration of lead exposure 25 years) whereas 14 did not (mean age 33, mean exposure 3 years). Urinary kallikrein activity was absent or reduced in all the affected workers. Of the 14 unaffected workers, 6 had altered kallikrein and/or plasma renin activity. As the kallikrein-kinin system is linked to the renin-angiotensin system, these preliminary data suggest a possible renal mechanism for hypertension at high lead levels.

Beevers and McKiernan (1985) recently reported a study on 733 workers occupationally exposed to lead: of these, 422 had elevated blood lead levels (over 40 μg/dL), and their blood pressures were compared with those of 439 workers not occupationally exposed to lead. No differences were found in the prevalence of hypertension or in the mean blood pressure of two groups. Full details of this study have not yet been published.

b) Other Population Groups with High Lead Exposures

Those who consume illicit alcohol (moonshine) are exposed to high concentrations of lead, and form another high-exposure group. Heavy alcohol consumption has been associated, however, with blood pressure elevation

(Klatsky et al., 1977; Criqui et al., 1981; Saunders et al., 1981; Gordon and Kannel, 1983), and is thus a confounding factor in studies of moonshine and blood pressure. For example, Peitzman et al. (1985) found that 64% of 200 male hypertensive veterans surveyed in Philadelphia admitted to past repeated ingestion of illicit alcoholic beverages. However, they used no control group and could not separate the effects of alcohol from the possible effects of lead.

Another study of moonshiners attempted to show an interaction between lead and the renin-angiotensin system. Sandstead et al. (1970) measured plasma renin activity (PRA) and aldosterone secretion rates (ASR) in nine men with lead intoxication (eight from moonshine and one battery factory worker). A high-sodium diet for 5 days was followed by ASR determination, and a low-sodium diet for 5 days with furosemide (120 mg) on the first day was followed by PRA and ASR determinations. There was mild hypertension in only one man. After the low-sodium diet, PRA did not increase to the normal range in eight out of the nine subjects and ASR did not increase to the normal range in seven out of the nine. Four men who were deprived of sodium for an additional 7-28 days did not have the expected increases in PRA or ASR. The authors suggested that lead interfered with the normal release of renin by the juxtaglomerular apparatus in response to sodium restriction or decreased intravascular volume. However, it is unclear how this might relate to lead-induced hypertension. Interpretation of this study is further complicated by the potentially confounding effect of alcohol.

The link between hypertension, lead and renal function was further explored by Batuman et al. (1983). They performed a 3-day EDTA lead-mobilization test on 70 Armed Services veterans, aged 23-70, who were recruited from the renal and hypertension clinics of a New Jersey Veterans Administration Medical Center. The cases were 48 patients with essential hypertension (40 of whom reported possible past exposure to lead from either industrial sources or consumption of moonshine); controls were 22 patients with renal disease. Cases and controls were not clearly different groups because 27 of the 48 patients with hypertension had impaired renal function and, of the 22 control patients with renal disease of known cause, 15 had hypertension. Excess mobilizable lead was significantly more frequent in patients with essential hypertension and renal impairment (18 of 27 patients) than in either patients with normal renal function (2 of 21) or control patients with renal disease (5 of 22). Blood lead levels, however, did not differ among the three groups.

This study suggests that occult lead absorption, as assessed by excess mobilizable lead, may have contributed to both hypertension and renal insufficiency in this group of patients. It also shows the difficulty of trying to assess past exposures to lead by means of blood lead levels. The EDTA lead-mobilization test is a more sensitive indicator of excessive body stores of lead, but is not a test that can be used on large groups of people.

Studies on Children

Three studies have been reported on blood pressure in children with varying lead levels. Only one reports an association between these factors, and it is found at high blood lead levels. All three studies involve small populations (34-80 children).

Rogan et al. (1978) identified 80 children by chart review from a Periodic Screening Detection and Treatment Program who had age, sex, race, blood pressure and blood lead levels recorded on the same visit. The children were 1-8 years of age. Blood lead levels ranged from 7 to 66 μg/dL, with a mean of

24 μg/dL. Analysis was restricted to 67 black children. Among children with blood lead levels under 15 (n = 8), 16-28 (n = 39) and over 39 μg/dL, mean systolic blood pressures were 87, 92 and 87 mmHg, respectively and mean diastolic pressure were 52, 59 and 50 mmHg, respectively. The authors concluded that there is a negative relationship between blood pressure and blood lead levels, the only significant results being the decline in blood pressures over a level of 29 μg/dL. However, if lead exerts its major effect on blood pressure levels below 15 μg/dL, one needs to compare the children with these low levels with children with higher levels. Unfortunately, there were only eight children in this study with lead levels under 15 μg/dL. Although the blood pressures in that small group of children are lower, the small numbers make it difficult to draw any conclusions. The fact that no confounders were controlled for, not even age, also makes interpretation of this study difficult.

In 1979 Jhaveri et al. reported on blood pressures in 34 children aged 1-3 years who were referred because of blood lead levels greater than 40 μg/dL. Thirty-four children with blood lead levels less than 40 μg/dL on routine screening were used as controls. In the low-lead group mean blood pressures were 74/54, compared with 95/60 in the high-lead group. The two groups of children were matched for age, height, weight, hematocrit and ethnic background. The differences in systolic pressure were significant ($p < 0.01$), despite the small numbers of children. It must be noted that the high-lead group in this study consisted of children with blood lead levels currently regarded as toxic.

Friedlander et al. (1981) also examined whether blood pressure correlates with body lead burden in children. They administered penicillamine to

38 children who had previously undergone one or more EDTA mobilization trials. They measured serum lead, free erythrocyte protoporphyrin (FEP), creatinine and hematocrit, and did a 6-h urine collection for lead and creatinine. After adjusting for age, sex, height and weight, none of the three lead measures (serum lead, FEP and lead mobilization) was significantly correlated with blood pressure. Again, the children in this study had relatively high blood lead levels, (mean 24.68, SD 6.27 μg/dL). Negative results in such a small study, however, are inconclusive.

Studies on Adults

A study conducted on 89 Boston policemen was recently reported by Weiss et al. (1986), who related blood lead levels at one point in time to blood pressure measurements taken 3, 4 and 5 years later. A tendency was observed for higher blood pressures to develop in subjects with initially higher blood lead levels. The authors interpreted their statistical analysis to mean that this tendency applies in particular to systolic blood pressure and to blood lead levels above 30 μg/dL (versus 20-29 μg/dL).

Ecological Studies

Two studies published in 1973 taken together provide some evidence of a relationship between lead and blood pressure. Stitt et al. (1973) reported on blood pressure levels in 244 male civil servants aged 40-65 in six towns in the United Kingdom with hard water, and 245 males in six towns with soft water. Lead pipes have been used extensively in the United Kingdom for water distribution, and several studies have shown a relationship between soft water and higher blood lead levels (Crawford and Clayton, 1973; Beevers et al., 1976; Thomas et al., 1979; Elwood et al., 1983). In Stitt et al.'s (1973) study, the mean blood pressure was higher in the soft-water group, the most significant difference being in the casual diastolic blood pressure. Crawford and Clayton (1973) studied bone lead and lead in the drinking water in these same 12 towns. Bone lead was assessed on necropsy cases. Mean bone lead content was much higher in the ribs of the deceased in the soft-water towns, although the water samples did not differ in lead concentration. These two studies taken together suggest that populations with high bone lead may also have higher blood pressures. However, these are ecological studies with measurements not done on the same people, and they are subject to all the fallacies of ecological studies. Specifically, in this case, there are many minerals with different concentrations in hard and soft water, some of which have been implicated in hypertension.

Human Epidemiological Studies

Sparrow et al. (1984) measured trace metals in the tap water in the homes of 246 male participants in the Normative Aging Study. Anyone with a blood pressure greater than 140 systolic or 90 diastolic in 1963 was excluded from the study. Blood pressures were then measured on each study participant every 3-5 years from 1963 to 1976. The blood pressure taken closest in time to the date of water sampling was used for the analysis. Analysis of covariance using age and body mass index as covariates showed no differences for systolic and diastolic blood pressures between the various lead exposure groups. Stratifying by educational level and town of residence did not change the results. In interpreting these negative findings, it must be remembered that the exclusion of hypertensives in 1963 may have excluded some of the individuals whose blood pressures were most sensitive to environmental factors. Water for analysis was collected on just 1 day, sometimes several years from the date of blood pressure measurement. Blood lead levels are a crude measurement of total body burden of lead, but tap-water lead levels are several times further removed from the measure of interest. Studies which have shown a relationship between water lead and blood lead levels and between blood lead level and hypertension have still failed to show a direct relationship between water lead level and hypertension.

A second epidemiological study which has failed to show a relationship between blood pressure and lead was reported by Staessen et al. (1984). They measured 24-h urinary excretion of lead and the excretion of retinol binding protein in spot urines in a random 4% sample of the population of a small Belgian town. Among 185 respondents over the age of 10, 51 were below the age of 20. In none of the age-sex groups did urinary lead and retinol binding protein contribute to the variability in blood pressure; however, there were only approximately 20 people in each age-sex group. Urinary lead excretion can remain constant over a wide range of lead intake, and it is not a very good measure of body burden of lead in humans.

Beevers et al. (1976) were the first to report a positive association in humans between blood lead levels and blood pressure levels in a sample of the general population. They examined blood and tap-water lead levels in 135 hypertensives and 135 age- and sex-matched controls selected from a screening survey conducted among Renfrew residents aged 45-64. Mean blood lead concentrations among hypertensive males were 26.2 ± 10.8 μg/dL and among normotensives 22.8 ± 7.6 μg/dL. In females the mean blood lead concentrations were 21.8 ± 10.8 μg/dL in hypertensives, compared with 18.8 ± 7.8 μg/dL in normotensives. High blood lead levels were found in 8.2% of hypertensives and 1.5% of normotensives. No correlation was found between blood pressure and blood lead level among the hypertensives, and no correlation was found between plasma creatinine and blood lead level. The influence of confounding variables (i.e. smoking, drinking, etc.) was not studied. Again, the lead levels reported in this study are fairly high. Compared with subjects with blood lead levels below 30 µg/dL, the prevalence of hypertension was about twice as high for subjects in the range 30-39 µg/dL and 10 times as high for those with levels above 40 µg/dL. Inferences to much lower blood lead levels are impossible.

In 1982 Moreau et al. reported on blood lead level and blood pressure in 431 members of the Paris police department. These were men, aged 24-55, who had not been treated for hypertension. They were examined during routine medical visits, and questioned about daily consumption of wine and tobacco. Statistical analyses of the data were done on the logarithm of blood lead level. Blood lead levels correlated significantly with blood pressure, age, wine and tobacco, and the association with systolic blood pressure persisted after controlling for the other variables, as well as body mass index. Diastolic blood pressure was also significantly related to blood lead but the association was weaker. The correlation between blood lead level and blood pressure was much stronger in young adults, and weakened with age. The relation was highly significant at ages 24-34, but not significant at ages 45-55. The authors hypothesized that the increase in blood lead concentration parallels the increase in blood pressure until some limit value, so that the trend is apparent only when other factors such as age do not competitively increase blood pressure by greater amounts. This would be a similar situation to that found with other risk factors such as obesity, where the effect is more marked in the younger population.

Kromhout et al. (1985) investigated the relationship between trace metals in blood and coronary heart disease risk factors in a sample of 152 men of the Zutphen cohort, aged 57-76. Blood lead level was significantly related to both systolic and diastolic blood pressure. The relationship with systolic pressure was somewhat stronger (standardized regression coefficient = 0.24) than with diastolic pressure (coefficient = 0.18). Both relationships were only slightly reduced when age and body mass index were controlled for.

A pilot case-control study by Khera et al. (1980) showed higher lead and cadmium blood levels in hypertensives and in patients with cardiovascular disease than in normotensive controls. However, this was only a pilot study; no confounders were controlled for, and no statistical tests performed.

Pocock et al. (1984) reported blood pressures of 7371 men in Britain, and classified them by blood lead levels. The correlation coefficient for the entire data set was close to zero, and the authors concluded that there was no relationship between blood lead level and blood pressure in their study. However, examining the data by the classifications of blood lead levels which they provide, a significantly higher prevalence of hypertension is apparent at blood lead levels above 16 μg/dL (24% of 2006) compared with lower levels (20% of 5365).

These authors have recently reanalysed their data using multiple regression techniques and controlling for body mass index, social class, age, alcohol, smoking, observer and location. In the case of systolic blood pressure, the unadjusted regression coefficient for log blood lead is statistically significant, but the coefficient is no longer significant when all the confounders except location (town) are controlled for. However, adding location to the models increases the statistical significance of the coefficient for log blood lead. For diastolic blood pressure the regression coefficient for log blood lead is significant only when location is included in the model. The authors still feel that the association between blood lead level and blood pressure is very weak and likely not causal.

Summary of the Human Studies

Variations of blood pressure with blood lead levels have been found both in special groups with high lead levels and in samples representative of the general population. Most of the published studies do show a relationship between blood lead level and blood pressure. The ones that do not are generally small studies or do not directly measure lead levels. However, the tendency to publish positive findings must not be overlooked. In particular there would have been no reason to publish negative findings prior to Beevers et al.'s (1976) report that a relationship between blood pressure and blood lead level existed.

The studies cited above have focussed on males (with the exception of Beevers et al. and the studies on children). There are almost no data on blood pressure at different lead levels in adult women. It is also noteworthy that, as in the animal studies, the relationship between blood lead level and blood pressure has been found at a variety of blood lead levels.

The above literature review provides us with a background against which we can view the recent studies by Harlan et al. (1985) and Pirkle et al. (1985).

Blood Pressure and Blood Lead in the NHANES Population

In 1985 Harlan et al. reported that there was a positive association between blood pressure and blood lead levels in the NHANES II population of adolescents and adults, ages 12-74, males and females, whites and blacks. The NHANES II data set is considered to be a well-validated one with adequate quality control for blood lead determinations and blood pressure measurements. Blood pressure was measured three times for each participant: seated, supine and then seated again. The last blood pressure was used in the analysis. Two types of statistical analyses were done. First, men and women were categorized into normotensive and hypertensive and the mean blood lead levels were compared between these two groups. Second, multiple linear regression models were used to explore the joint relationships among selected variables and blood pressure. Thirty-four variables had significant univariate correlations with blood pressure. The unadjusted correlation coefficients between the natural logarithm of blood lead and diastolic blood pressure for white and black women were 0.11 and 0.22 ($p < 0.0005$), respectively, and for white and black men 0.16 and 0.11 ($p < 0.001$), respectively.

Subjects were then separated into two age groups, 21-55 and 56-74. Blood lead levels were significantly higher in younger men and women with high diastolic pressures, but they were not significantly different for any of the blood pressure categories in the older age group.

In the multiple regression equations, blood lead level had a significant relationship to systolic and diastolic blood pressure which was independent of the relationship between other variables in men, but not in women. Dietary calcium was related to both lead and blood pressure: when lead and dietary calcium were both included in the model, lead entered the regression equation for men, and calcium entered for women. Thus an independent relationship between lead and blood pressure was shown only in men.

Pirkle et al. (1985) further analysed the same data set, restricting their analyses to white men, ages 40-59. They used weighted stepwise multiple linear regression to determine which variables were significantly related to blood pressure, and then incorporated the design effects of the study. Almost all the nutritional and biochemical variables in the NHANES II were included in the stepwise regression. Squared and natural logarithmic transformations of the variables were also included. In addition, the following variables were evaluated for their potential effect on the significance of blood lead level: urban/rural status, income, educational level, season of the year, region of the country, triceps skinfold thickness, family history of hypertension, antihypertensive medication use, amount of exercise and cigarette and alcohol consumption.

The final regression equation for systolic blood pressure included the following variables: age, age-squared, body mass index, dietary potassium, hemoglobin, dietary vitamin C, blood lead level (logarithmic scale) and albumin. For diastolic blood pressure, hemoglobin and dietary potassium were not included in the model, but dietary riboflavin, dietary oleic acid and serum vitamin C were. The age variables had to be forced into the models, as there was no relation of age to blood pressure over this restricted age range.

This study uses a well-validated data base, and rigorous and thorough statistical analyses. The association between blood lead level and blood pressure was extremely robust: the regression coefficients (i.e. the magnitude of the association) varied by only about 10% across the many regression models studied.

Criticisms of the study generally centre around the problem of unknown confounding factors. For example, lead could be a surrogate marker for some socio-economic variable which was not controlled for or poorly measured. Other toxic metals, such as cadmium (Perry and Erlanger, 1978; Voors et al., 1982), which were not measured, may covary with lead, and be related to hypertension.

The problem of unknown confounding factors exists in every study. For those confounders which have not been measured, only a new study can address the issue. For those potential confounders which are in the data set, reanalysis of the data can answer the criticisms. The authors have reanalysed the data entering date of examination as a variable in the regression equations (Schwartz, 1985a). This somewhat diminished the size of the lead coefficient, but it nevertheless remained significant. As well, 32 dummy variables were entered into the regression equation for the 32 socio-demographic strata which were used as the basis of sampling (Staessen et al., 1984). These analyses were performed on all males over age 20. Lead remained significantly associated with blood pressure after inclusion of these variables. Stratifying the data by the 2-year period of the study in which the examination took place also did not affect the size of the regression coefficients.

The US Environmental Protection Agency submitted the paper by Pirkle et al. (1985) to a panel of independent scientists for peer review. Some found the results acceptable as evidence for a probable causal association. In support of their opinions, they mentioned the good quality control of the study, the biological plausibility, the consistency with other human studies and animal experiments and the robustness of the association.

The majority of reviewers, however, questioned a causal relationship, primarily because NHANES was not designed to test a specific hypothesis about lead. In performing hundreds of analyses on the same data set, by chance 1 in 20 will be statistically significant at the 0.05 level. There is no way of sorting out the true results from the chance results. No corrections were made in this study for the large number of analyses performed.

Other reasons for questioning a causal relationship include the following:

- causality cannot be inferred from a cross-sectional study
- the response rate to the survey was only 60%, and the non-respondents were not a random subset of the targeted population; this could potentially lead to bias
- other human and animal studies are not entirely consistent
- a clear dose-response relationship does not emerge from the various studies
- calcium did not enter the regression equation when lead was excluded; this reduces the likelihood of competitive inhibition of divalent cation absorption, the one biologically plausible mechanism suggested by the authors.
- there were divergent results for subgroups defined by age, race and sex
- the authors failed to explore whether the relationship was driven by a few influential points
- bivariate analyses of blood lead levels and important variables such as alcohol intake, cigarette smoking and socio-economic status were not reported.
- the contribution of lead to the total variance of blood pressure was quite low (1.5%).

In an attempt to see if the relationship between blood lead level and blood pressure would hold up in another North American population, Neri and Hewitt (1986) analysed the data from the Canada Health Survey (CHS). This body of data has the distinct advantage of having been collected during a period of only 10 months (during 1978-79) rather than the 49 months that elapsed during NHANES II. The CHS sample comprises 2193 subjects, male and female, aged 25-64; the correlation coefficient was +0.115 ($p < 0.001$). Zinc and hemoglobin levels were found to be confounders and were included in multiple regression analyses together with sex, age and body build. The dependent variable presented was diastolic blood pressure. Subjects on antihypertensive medications were excluded. Blood lead level was used as measured and also in several log transformations. In all cases the significance of the association between blood lead level and diastolic blood pressure disappears when hemoglobin and zinc are added to the equations. The linear model provides the maximal effect, i.e. a 3-mm increase in diastolic blood pressure for a change of blood lead level from 0 to 47 µg/dL (the extreme values found in the CHS). The data were also analysed on a categorical level. The relative risk of having a diastolic blood pressure above 90 mmHg was 1.23 for individuals with blood lead levels above the median (10 µg/dL). Thus the results appear to be at least weakly supportive of the NHANES findings.

Discussion

To put some of the above comments into perspective, we found it useful to examine the potential causal nature of the association between blood lead levels and blood pressure in terms of Bradford Hill's (1965) criteria for causation. It should be remembered that not all criteria need be satisfied to infer a causal relationship, but that the inference of causality is strengthened if most of the criteria are met.

1) Strength of association. The stronger the association between two variables, the greater is the likelihood of a causal relationship. The asso-

ciation between blood lead level and blood pressure is moderately strong in white males in the NHANES data set (5 mmHg difference in mean diastolic blood pressure between blood lead levels of 7 and 30 μg/dL). However, the association is not strong in other data sets, and is quite difficult to demonstrate. In part, this is due to the lack of precision in both measurements of interest. Blood lead levels prior to the last 5 years are not generally considered reliable (Orssaud et al., 1985), and in many centres the lowest limit of detection is 10 μg/dL. Blood pressure, however accurately measured, is subject to considerable short-term variation within individuals. It therefore requires very large sample sizes in humans to overcome the 'noise effects' and ensure detection of an association.

2) Consistency. The repeated observation of an association by different persons, in different places, circumstances and times is an important consideration in inferring causality. We see such consistency in the mortality studies of lead workers. Studies at lower levels of blood lead are not as consistent, the main support in epidemiological investigations coming from Beevers et al. (1976) (but not Beevers and McKiernan, 1985), Moreau et al. (1982) and Kromhout et al. (1985). However, none of the negative studies has enough statistical power to refute the association.

3) Dose-response. The relationship between blood lead level and blood pressure is not well defined. In the NHANES population there was a linear relationship between blood pressure and the logarithm of blood lead level. Caution should be exercised in the interpretation of this dose-response curve, because the use of logarithms of the independent variable forces an infinite slope of the dose-response curve at the origin and a flat curve for large values of the independent variable. Extrapolation to both low and high levels

of blood lead is thus dangerous. The inference that there is little relationship between lead and blood pressure at blood lead levels above 20 µg/dL may therefore not be accurate.

It is difficult to determine from the literature at what blood levels of lead there might be a relationship to blood pressure. In the animal experiments, Perry and Kopp (1983) demonstrated this relationship using doses of 0.1 ppm lead in water. They considered 25 ppm lead to be a high dose, a level at which the relationship tends to disappear. On the other hand, Victery et al. (1982) demonstrated the relationship by feeding rats 100 ppm lead in water, and considered 500 ppm to be a high dose.

In human studies, we find the same situation. Those investigators who have shown a positive association have done so at widely differing levels of blood lead. The majority of them, however, found the association at levels much higher than those indicated by the NHANES survey, in which the mean increment of blood pressure per unit increase in blood lead is largest in the range of 5-10 µg/dL lead in the blood. Thus there is no indication from the literature as to the correct form of dose-response relationship.

4) Chronology. It is impossible to prove a chronological relationship in a cross-sectional study. Cohort studies, following groups of people with different lead levels, and experimental studies, observing the effect of eliminating lead from the environment, have not to date been performed in humans. Thus none of the human studies has addressed the issue of chronology. The only evidence that exposure to lead precedes the onset of hypertension comes from studies on animals. Here, the temporal relationship is clearly demonstrated.

5) Specificity. Specificity refers to the one-to-one relationship bet-

ween exposures and diseases. It is a useful concept in infectious disease, but less helpful with chronic diseases. The effects of lead are certainly not specific to blood pressure, nor would we expect them to be.

6) Biological plausibility. It is helpful if a suspected cause-effect relationship makes biological sense. The current review has shown that the association between lead and blood pressure is certainly biologically plausible. At low lead levels the most likely mechanism is stimulation of excitation contraction coupling by interference with calcium metabolism in vascular smooth muscle.

One aspect which is not biologically plausible to some is the lack of an association in females. In general, there are very few data on females. In the NHANES population, there is a positive association between lead and blood pressure in females, but it fails to remain statistically significant when all the confounding variables are assessed. It is possible that the association is not qualitatively different in females, but just weaker, as the strength of associations often differs between age and sex subgroups.

7) Experiment. The NHANES data have been supported by experimental evidence in animals, as reviewed above. Intervention trials in humans (decreasing lead exposure) would be more helpful in demonstrating causation, but have not been done.

8) Analogy. There are analogous situations whereby toxins, e.g. cadmium, produce hypertension at low levels, with blood pressure reverting to normal at 'toxic' levels (Perry and Kopp, 1983). Also, a hypertensive effect has been established for two metals which have structural characteristics similar to lead, i.e., mercury (Bradford Hill, 1965) and cadmium (Schroeder, 1965; Harvey, 1975). A third such metal, thallium, may also cause hyperten-

sion (Bank et al., 1972).

The association between lead and blood pressure would appear to meet many of the criteria for the inference of causality. The most important criterion that is not met is a clear dose-response relationship. There is also some lack of consistency between studies. A cross-sectional study, however well performed, can provide only weak evidence for causality. The evidence is even weaker if the study was not designed to test the specific hypothesis. Previous studies strengthen the inference of causality of the association, but it is by no means established.

Summary

There is evidence from animal studies that exposure to lead can produce hypertension in rats, and that a plausible physiological basis exists for this effect. Human studies of populations with high exposures to lead consistently show excess mortality from cerebrovascular disease and renal disease, but fail to show an increased prevalence of hypertension among lead workers. The major epidemiological study to show an association between lead and blood pressure, NHANES, is a well-performed study, but was not designed to test the hypothesis. Its results are supported by three European epidemiological studies, but fail to receive support from several other investigations. The association between lead and blood pressure currently must be viewed as a plausible hypothesis which requires confirmation.

Policy Implications

It would be premature to base national policy solely on the purported association between lead and blood pressure. Even if the relationship is shown to be real and causal, the effects on the blood pressure of Canadians are not known, as a dose-response relationship has not been established.

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23. ASSESSMENT AND MANAGEMENT OF RISK ASSOCIATED WITH AIRBORNE LEAD IN THE UNITED STATES: KEY ISSUES IN THE 1970's AND 1980's

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Introduction

The assessment and management of risks associated with airborne lead became a major focal point for debate from among numerous environmental problems addressed by the United States in the 1970's. Control of airborne lead exposure as a public health problem has been the responsibility of the US Environmental Protection Agency, as mandated under various sections of the 1970 Clean Air Act (USC, 1982) and its 1977 Amendments (Stat., 1977). The EPA has approached the regulation of airborne lead via two main avenues: (i) the establishment and enforcement of a National Ambient Air Quality Standard (NAAQS) for lead, and (ii) the phase-down of the use of lead in gasoline, as the single largest and most widespread source of airborne lead in the United States. The present chapter concisely summarizes some of the main considerations taken into account by the US EPA in following these two parallel courses of action in dealing with airborne lead as a public health problem in the 1970's. This chapter also highlights key issues that are shaping debate on the subject of airborne lead control as the United States continues to deal with the problem in the 1980's.

Establishment and Compliance with the 1978 NAAQS for Lead

The current NAAQS for lead was established in 1978 as 1.5 $\mu g/m^3$ (averaged over 90 days) to protect public health. The scientific basis for that standard was evaluated in the EPA criteria document, Air Quality Criteria for Lead (EPA, 1977), published in December 1977. Simultaneously with publication of the criteria document, alternative rationales proposed for the setting of the NAAQS were described in the US Federal Register (Anonymous, 1977). The ultimate form and level of the lead NAAQS were selected after public hearings held in 1978 to receive comments on the proposed standard, and the rationale for promulgation of the 1.5 μg/m^3 lead NAAQS was described in the 1978 formal rule-making announcement which appeared in the Federal Register (Anonymous, 1978) later that year.

The five main components of the rationale underlying the 1978 lead NAAQS are summarized in Table 1. Briefly, the 1.5 μg/m^3 standard was based upon (i) determination of 30 μg/dL of blood lead (PbB) as the 'maximum safe level' for exposure of any given child, (ii) protection of 99.5% of the 6-year-old and younger pediatric population of the United States as a group most at risk,

Table 1.

Rationale for current lead NAAQS based on five main components.

1) Definition of 'maximum safe' blood lead (PbB) level for members of population at greatest risk (children under 6 years old): 30 μg/dL.

2) Delineation of form and key parameters of blood lead distribution for pediatric populations in the US: log normal, geometric SD = 1.3.

3) Policy decision on 99.5% of at-risk group to be kept under 30 μg/dL and resulting target pediatric population geometric mean: 15 μg/dL.

4) Determination of 12 μg/dL blood lead as typical contribution from non-air (direct inhalation) sources such as water, diet, dust, etc.

5) Current NAAQS of 1.5 μg/m^3 defined as allowable direct air (inhalation) exposure resulting in 3 μg/dL blood lead contribution based on air lead/blood lead ratio of 1:2.

(iii) determination of a 1.3 geometric standard deviation for the log normal distribution typical of pediatric blood lead levels in United States populations, and (iv) selection of 15 μg/dL PbB as the geometric mean target value for keeping 99.5% of the children below the 30 μg/dL PbB 'maximum safe level.' Non-air sources were estimated to contribute approximately 12 μg/dL PbB to pediatric blood lead levels, leaving 3.0 μg/dL PbB as being allowable from air. Evaluation of available epidemiological data on air lead - blood lead relationships supported a typical 1:2 linear relationship of air lead (in $\mu g/m^3$) to blood lead levels (in μg/dL) for children. Dividing the 3.0 μg/dL PbB allowable from air by 2 results in the value of 1.5 $\mu g/m^3$ air lead being selected for the lead NAAQS.

Considerable controversy existed regarding the evaluation of scientific data bearing upon conclusions which ultimately resulted in the values specified in Table 1 being selected as part of the rationale for the 1978 lead NAAQS. It is beyond the scope of the present paper to discuss in detail the basis for selection of each of the selected values (see Anonymous, 1977, 1978 for detailed discussion). However, it is worth noting that, in each case, policy decisions had to be made by the US EPA Administrator from among various alternative values for each NAAQS rationale component--alternatives which were argued for by various private sector organizations (e.g. industrial trade associations, environmental interest groups, medical experts, other lead experts, etc.) and other government agencies in the United States. The choice of values selected by the Administrator was based on his best judgements given (i) inputs from the EPA staff (as contained in the 1977 Air Quality Criteria for Lead Document (EPA, 1977)), (ii) advice by the EPA's Science Advisory Board (a group of non-EPA scientific experts that provide independent peer review of EPA criteria documents and air regulatory decisions), and (iii) comments from private sector groups and other government agencies. The implied impacts on the standard of various choices of alternative values for key components of the NAAQS are illustrated in Table 2.

Table 2.

Impact of alternative policy choices for lead NAAQS rationale components on ultimate standard selected.

Selection of Safe Blood Lead (PbB) Level:

Max. Safe PbB Level ($\mu g/dL$)	Target Geom. Mean Level ($\mu g/dL$)	Implied Standard* ($\mu g/m^3$)
40	20	4.0
30**	15	1.5
20	10	0

Selection of Protected Population Percentage:

% of Population ≤ Max. Safe Level	Target Geom. Mean Level ($\mu g/dL$)	Implied Standard* ($\mu g/m^3$)
99.0	16	2.1
99.5	15	1.5
99.9	13	0.7

Determination of Non-Air Contribution to PbB:

Non-Air Contribution To Population PbB ($\mu g/dL$)	Implied Standard* ($\mu g/m^3$)
10	2.5
11	2.0
12**	1.5
13	1.0
14	0.5

Determination of Blood Lead ($\mu g/dL$) to Air Lead ($\mu g/m^3$) Ratio

Blood/Air Lead Ratio	Implied Standard* ($\mu g/m^3$)
1.4	2.1
1.6	1.9
1.2	1.7
2.0**	1.5
2.2	1.3

* Assuming all other Pb NAAQS components remained the same as actually selected in setting the NAAQS.

**Value actually selected, resulting in current Pb NAAQS of 1.5 $\mu g/m^3$.

As shown in Table 2, alternative choices for any of the various NAAQS rationale components listed could have resulted in distinctly different air lead concentrations being specified as the NAAQS for lead in 1978. However, the component probably exerting the single greatest impact on the ultimate selection of the standard (assuming all other components remained the same) was the definition of 30 μg/dL as the 'maximum safe blood lead level'. The main conclusions arrived at concerning lowest-observed-effect levels for key types of lead health impacts in young children are summarized in Table 3, as evaluated in the 1977 lead criteria document (EPA, 1977) based upon information available in the scientific literature at the time of its preparation and the setting of the 1978 NAAQS for lead. The blood lead values indicated for each type of effect in Table 3 are not meant to imply that all children experiencing those concentrations would experience the associated effect; rather, at least some children would be expected to manifest the particular effect at a given blood lead level or higher ones (based on reported research findings).

Much individual biological variation, due to many factors (e.g. nutritional status, genetic background, etc.), was recognized to exist, such that wide variations in blood lead values may be associated with the manifestation of particular lead effects in children. In other words, some children may experience the effects indicated in Table 3, only at much higher blood lead values than the lowest-observed-effect levels shown in the table. This complicates the selection of a maximum safe level, because it is difficult or impossible to determine *a priori* the blood lead level(s) at which any given child will experience a particular lead health impact. The definition of a maximum safe blood level, then, must be predicated on selection of a level (i) distinctly below any blood lead concentrations associated with clearly adverse health effects, and (ii) which incorporates a margin of safety large enough to

Table 3.

1977-78 evaluation of lowest-observed-effect levels for pediatric lead health effects (EPA, 1977).

Blood Lead Levels (μg/dL)	Hematopoietic And Heme Synthesis Effects	Central and Peripheral Nervous System Effects
80-100		Encephalopathic signs and symptoms
70	Frank anemia	
50-60		Cognitive (CNS) deficits Peripheral nerve dysfunction
40	Reduced hemoglobin	
30		
15-20	Increased erythrocyte protoporphyrin	
10	ALAD inhibition	

minimise adequately the probability of any individual child approaching blood lead levels associated with unacceptable risk of adverse effects.

The main factors or conclusions which served as the basis for the selection in 1977-78 of 30 μg/dL as the maximum safe blood lead level are summarized in Table 4. Major emphasis was placed at that time on (i) the avoidance of clearly adverse lead-induced effects on heme synthesis on blood-forming physiological processes (producing observed decrements in hemoglobin synthesis starting at 40 μg/dL and, ultimately, sufficiently impaired hemoglobin synthesis and red blood cell survival such that clinically recognized anemia occurs at about 70 μg/dL), and (ii) averting of clearly adverse nervous system effects (e.g., lead-induced cognitive deficits manifested in terms of lower IQ values or other behavioural abnormalities and peripheral nerve dysfunctions

Table 4.

Basis for selection of 30 μg/dL as 'maximum safe blood lead level'.

1) Increases in erythrocyte protoporphyrin (EP) levels starting at 15-20 μg/dL indicative of impaired heme synthesis at least in red blood cells but not clearly adverse effect.

2) More marked increases in EP levels at 30-40 μg/dL indicative of clearly abnormal heme synthesis decrements.

3) Reduced hemoglobin synthesis at 40 μg/dL and nervous system deficits at 50-60 μg/dL as clearly adverse effects.

4) 30 μg/dL criterion level allowed margin of safety against hemoglobin reductions and nervous sytem effects.

reflected by slowed nerve conduction velocities), demonstrated at 50-60 μg/dL PbB as of 1977-78. Concern existed regarding possible more wide-ranging effects of lead on heme synthesis (see Figure 1) in additional tissues and organs besides those involved with blood cell formation and the synthesis of hemoglobin and, possibly, at levels below 30 μg/dL. However, insufficient evidence demonstrating such wide-ranging lead effects on heme synthesis at low lead levels was judged to exist to support more stringent regulatory actions based on a lower maximum safe blood lead level for children. The same also applied then in regard to concerns about lower blood lead levels possibly being associated with overt or non-overt manifestations of lead effects on nervous system functioning.

Despite court challenges to the NAAQS for lead, which followed shortly after setting the standard in 1978 but which were resolved in favor of the US EPA, considerable progress has been made in attaining the 1.5 $\mu g/m^3$ standard during the past 5 years. Figure 2 shows trends in ambient air lead levels monitored at urban sampling stations from 1966 to 1980, with marked decreases

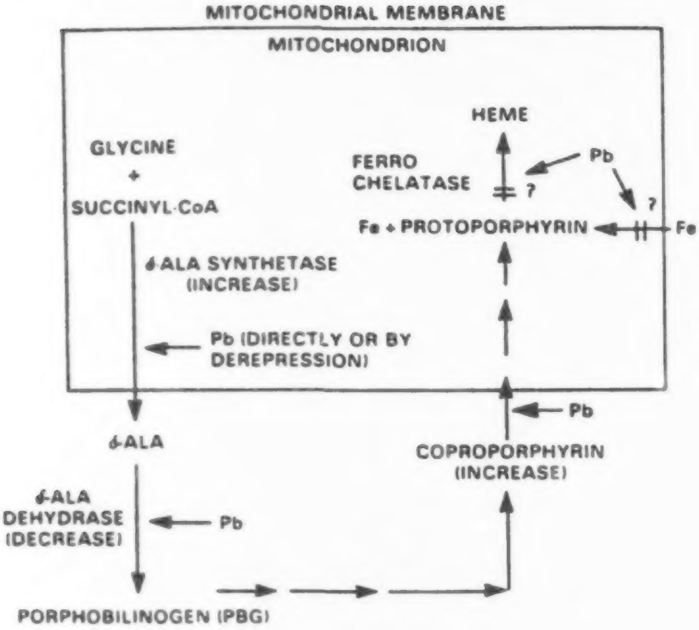
MITOCHONDRIAL MEMBRANE
MITOCHONDRION
HEME
GLYCINE
+
SUCCINYL·CoA
FERRO CHELATASE
?
Pb
?
Fe + PROTOPORPHYRIN
Fe
δ-ALA SYNTHETASE (INCREASE)
Pb (DIRECTLY OR BY DEREPRESSION)
Pb
δ-ALA
COPROPORPHYRIN (INCREASE)
δ-ALA DEHYDRASE (DECREASE)
Pb
PORPHOBILINOGEN (PBG)

Figure 1 Lead effects on heme biosynthesis.

evident in numbers or percentages of total stations reporting air lead concentrations above 1.0 μg/m^3 since 1977-78 and an increase in monitoring stations with annual averages below 0.5 μg/m^3 since that time. This progress in reduction of airborne lead in urban areas and at other sites, such as around lead smelters, in rural areas is partly due to (i) implementation of stationary source controls at emission sites such as mines, smelters, and alkyl lead

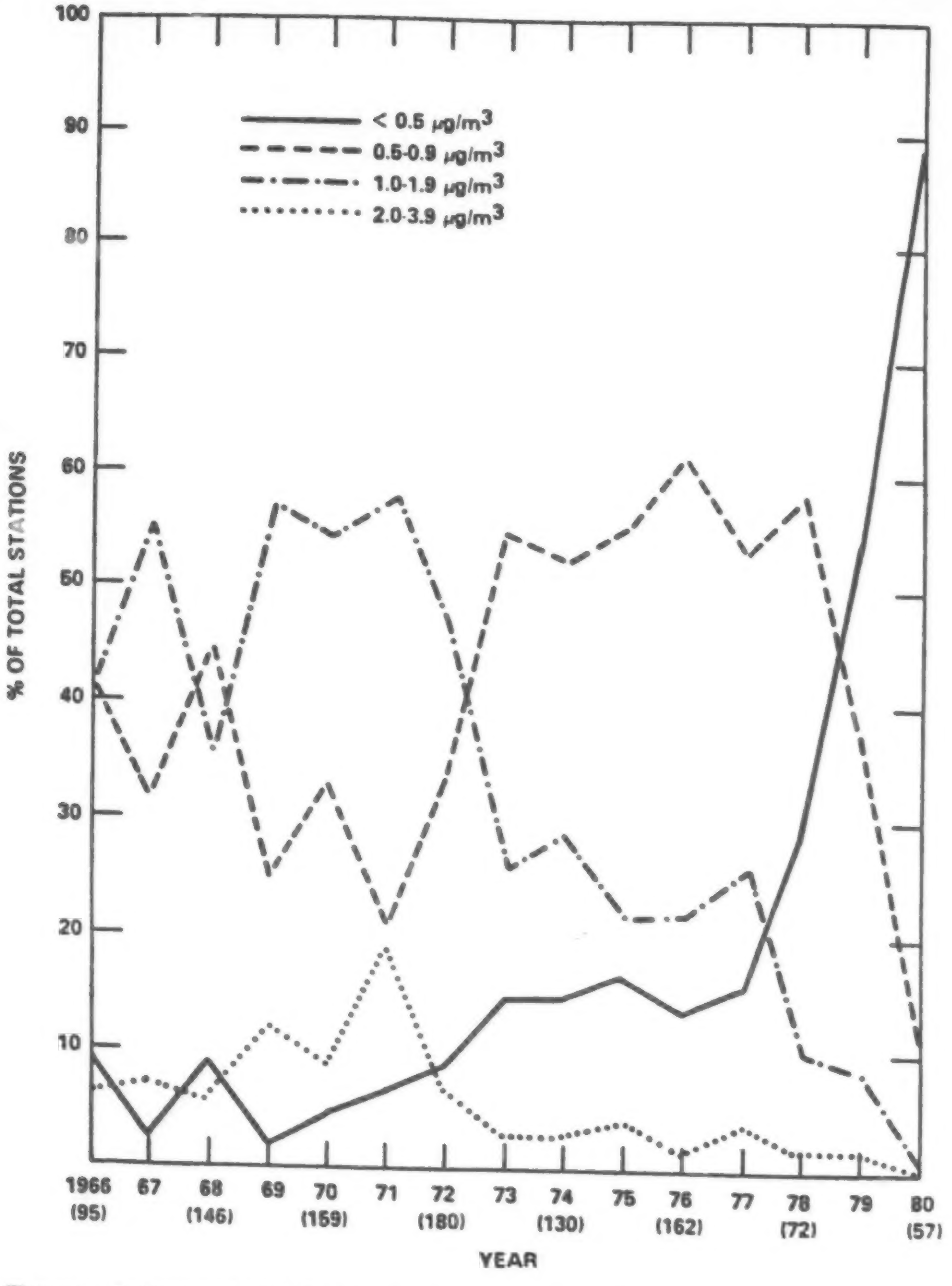

Figure 2. Percent of urban stations reporting indicated concentration interval.

plants, (ii) the closing or decreasing of commercial operations at some of the emission sites, and (iii) the phase-down of lead in gasoline as the most widespread source of airborne lead in the United States (see below for discussion of this latter factor).

Re-evaluation of the NAAQS for Lead

The 1977 Clean Air Act Amendments (Stat., 1977) mandate that periodic review of criteria and revision, as appropriate, of the NAAQS's for each of the pollutants regulated under Sections 108 and 109 of the Act be carried out at least every 5 years by EPA. The mandated 5-year review of criteria for the lead NAAQS commenced in 1982 with the initiation of updating and revision of the lead criteria document. The first External Review Draft (EPA, 1983) of the revised document was released in October 1983 for public comment, followed by its peer review in April 1984 by the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board. Another draft has since been prepared, taking into account public comments on the first draft as well as CASAC advice. The second External Review Draft (EPA, 1984), released in October 1984 for public comment, was reviewed by CASAC in public session in May 1985, and is to be followed by final revision of the document and its publication in 1986. An EPA staff paper that details the development of resulting revisions in the rationale for the lead NAAQS is also in preparation by the EPA's Office of Air Quality Planning and Standards (OAQPS), based on the criteria document evaluations; that staff paper is expected to undergo CASAC peer review and, ultimately, publication in essentially the same time frame as the revised EPA Air Quality Criteria for Lead document.

A number of key issues addressed in the revised criteria document can already be identified as likely to have crucial bearing on ultimate decisions concerning the possible revision of the NAAQS for lead. For example, the determination of a 'maximum safe blood lead level' for pediatric exposures has again been a major focal point of controversy, and is expected to be one of the main driving forces in determining the final form and level of any revised NAAQS for lead. In addition, certain new concerns have been raised regarding health effects in adults, which are likely to play a major role in decision-making on the NAAQS.

Lead-induced Health Effects in Children

Table 5 summarizes many of the key conclusions tentatively reached thus far in the most recent draft (EPA, 1984) of the revised criteria document in regard to lowest-observed-effect levels of lead-induced health effects in children. Several changes should be noted in Table 5 in comparison with the earlier table (Table 3) illustrating lowest-observed-effect levels at the time of the 1977-78 evaluation of available evidence on lead-induced health effects.

First, note that the previous conclusions regarding levels at which heme synthesis and hematopoietic (blood cell formation) effects occur still stand and, in fact, have been reinforced by additional evidence. Also, additional hematological effects have been demonstrated at extremely low lead levels, i.e. pyrimidine-5'-nucleotidase (Py-5-N) activity inhibition in red blood cells starting at PbB levels below 10 μg/dL and with no evident threshold.

Note also that additional data now exist that are indicative of central nervous system (CNS) cognitive effects at approximately 30-50 μg/dL PbB (and likely somewhat below), as well as of peripheral nerve dysfunction (as indexed by slowed nerve conduction velocities (NCV)) at levels as low as 30 μg/dL. Altered CNS electrophysiological responses (e.g. electroencephalographic (EEG)

Table 5.

Summary of lowest-observed-effect levels for key lead-induced health effects in children.

Lowest-Observed Effect Level (PbB)	Heme Synthesis and Hematological Effects	Neurological Effects	Renal System Effects	Gastrointestinal Effects
80 - 100 µg/dL		Encephalopathic signs and symptoms	Chronic nephropathy (aminoaciduria, etc.)	Colic, other overt gastrointestinal symptoms
70 µg/dL	Frank anemia			
60 µg/dL		Peripheral neuropathies		
50 µg/dL				
40 µg/dL	Reduced hemoglobin synthesis	CNS cognitive effects (IQ deficits, etc.)		
	Elevated coproporphyrin	Peripheral nerve dysfunction (slowed NCV's)		
	Increased urinary ALA			
30 µg/dL			Vitamin D metabolism interference	
15 µg/dL	Erythrocyte protoporphyrin elevation	Altered CNS electrophysiological responses		
10 µg/dL	ALA inhibition			
	Py-5-N activity inhibition			

Abbreviations: PbB = blood lead concentrations; Py-5-N = pyrimidine-5'-nucleotidase; NCV = nerve conduction velocities; CNS = central nervous system; ALA = δ-aminolaevulinic acid.

brain wave patterns and evoked sensory potentials) have also been demonstrated at still lower PbB levels, with no evident threshold for some effects down to below 10-15 µg/dL.

Of particular additional importance is the newly demonstrated occurrence of lead interference with vitamin D metabolism, an effect thought to be mediated via lead effects on certain cells in the kidney. Vitamin D metabolism interference is but one of a growing number of wide-ranging health effects on various organ systems now becoming attributable to lead inhibition of heme synthesis in many different tissues and organs (as illustrated in Figure 3).

In summary, the available information assessed in the revised criteria document (EPA, 1984) demonstrates that there exists a continuum of biological effects associated with lead across a broad range of exposure. At very low levels of lead exposure, biochemical changes, such as disruption of certain enzymatic activities involved in heme biosynthesis and erythropoietic pyrimidine metabolism, are detectable. Heme biosynthesis is a generalized process in mammalian species, including man, with importance for normal physiological functioning of virtually all organ systems. With increasing lead exposure, there are sequentially more intense effects on heme synthesis as well as a broadening of effects on additional biochemical and physiological mechanisms in various tissues. In addition to heme biosynthesis impairment, disruptions of normal functioning of the erythropoietic and nervous systems are among the earliest effects observed as pediatric lead exposure levels increase. With increasingly intense exposure, more severe disruption of erythropoietic and neural functions occur, and additional organ systems are affected. At sufficiently high levels of exposure, nervous system damage and other effects can be severe enough to cause death or, in cases of non-fatal

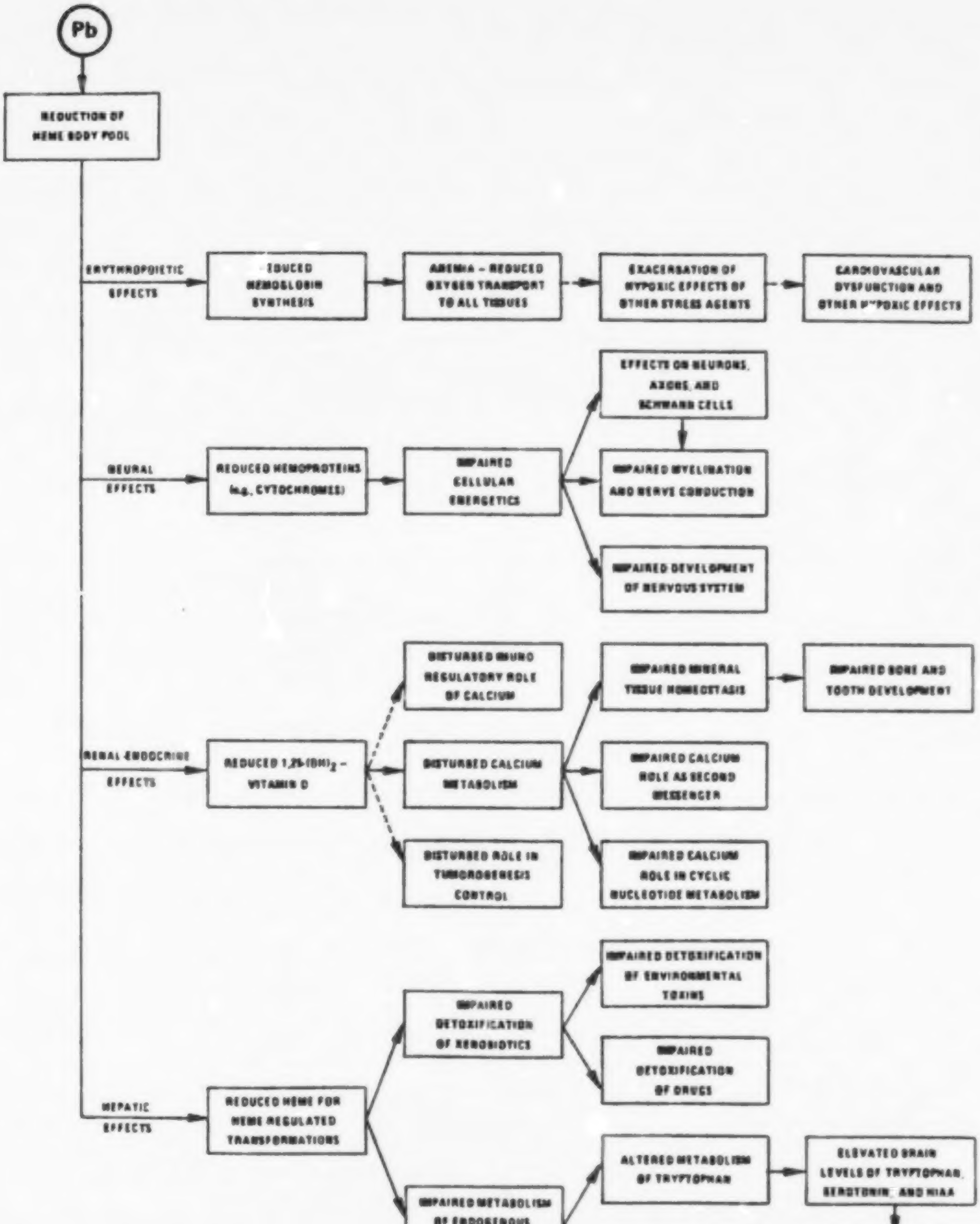
Pb
REDUCTION OF HEME BODY POOL
ERYTHROPOIETIC EFFECTS
REDUCED HEMOGLOBIN SYNTHESIS
ANEMIA – REDUCED OXYGEN TRANSPORT TO ALL TISSUES
EXACERBATION OF HYPOXIC EFFECTS OF OTHER STRESS AGENTS
CARDIOVASCULAR DYSFUNCTION AND OTHER HYPOXIC EFFECTS
NEURAL EFFECTS
REDUCED HEMOPROTEINS (e.g., CYTOCHROMES)
IMPAIRED CELLULAR ENERGETICS
EFFECTS ON NEURONS, AXONS, AND SCHWANN CELLS
IMPAIRED MYELINATION AND NERVE CONDUCTION
IMPAIRED DEVELOPMENT OF NERVOUS SYSTEM
RENAL-ENDOCRINE EFFECTS
REDUCED 1,25-(OH)$_2$ - VITAMIN D
DISTURBED IMMUNO REGULATORY ROLE OF CALCIUM
DISTURBED CALCIUM METABOLISM
DISTURBED ROLE IN TUMOROGENESIS CONTROL
IMPAIRED MINERAL TISSUE HOMEOSTASIS
IMPAIRED BONE AND TOOTH DEVELOPMENT
IMPAIRED CALCIUM ROLE AS SECOND MESSENGER
IMPAIRED CALCIUM ROLE IN CYCLIC NUCLEOTIDE METABOLISM
HEPATIC EFFECTS
REDUCED HEME FOR HEME REGULATED TRANSFORMATIONS
IMPAIRED DETOXIFICATION OF XENOBIOTICS
IMPAIRED DETOXIFICATION OF ENVIRONMENTAL TOXINS
IMPAIRED DETOXIFICATION OF DRUGS
IMPAIRED METABOLISM OF ENDOGENOUS AGONISTS
ALTERED METABOLISM OF TRYPTOPHAN
ELEVATED BRAIN LEVELS OF TRYPTOPHAN, SEROTONIN, AND HIAA
DISTURBED INDOLEAMINE NEUROTRANSMITTER FUNCTION
IMPAIRED HYDROXYLATION OF CORTISOL

Figure 3. Multi-organ impact of reductions of heme body pool by lead. Impairment of heme synthesis by lead results in disruption of a wide variety of important physiological processes in many organs and tissues. Particularly well documented are erythropoietic, neural, renal-endocrine, and hepatic effects indicated above by solid arrows (⟶). Plausible further consequences of heme synthesis interference by lead which remain to be more conclusively established are indicated by dashed arrows (⇢).

Source: U.S. EPA, 1984

lead poisoning, long-lasting sequelae such as mental retardation. All of these types of lead health effects are of importance in providing an overall picture of the element as a general systemic toxicant, as discussed in much detail in the revised EPA Air Quality Criteria for Lead document (EPA, 1984).

Lead-induced Health Effects in Adults

Lowest-observed-effect levels (in terms of blood lead concentrations) associated with particular health effects of concern for human adults in relation to specific organ systems or generalized physiological processes, e.g. heme synthesis, are summarized in Table 6, adapted from the most recent draft of the revised EPA lead document (EPA, 1984). That table should be viewed as representing lowest blood lead levels thus far credibly associated with unacceptable risk for a given effect occurring among at least some adults. As such, many adults may not experience the stated effect until much higher blood lead levels are reached, due to wide ranges of individual biological susceptibility, variations in nutritional status, and other factors.

Among the most serious effects associated with markedly elevated blood lead levels are severe neurotoxic effects that include irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathic symptoms. For most human adults, such damage typically does not occur until blood lead levels exceed 100-120 µg/dL. Often associated with encephalopathic symptoms at such blood lead levels are severe gastrointestinal symptoms and objective signs of effects on several other organ systems. Precise threshold(s) for occurrence of overt neurological and gastrointestinal signs and symptoms of lead exposure in cases of subencephalopathic lead intoxication remain to be established, but such effects have been observed in adult lead workers at blood lead levels as low as 40-60 µg/dL, notably lower than levels

Table 6.

Summary of lowest-observed-effect levels for key lead-induced health effects in adults (EPA, 1984).

Lowest-Observed Effect Level (PbB)	Heme Synthesis and Hematological Effects	Neurological Effects	Effect on the Kidney	Reproductive Function Effects	Gastrointestinal Effects
100-120 μg/dL		Encephalopathic signs and symptoms	Chronic nephropathy		
80 μg/dL	Frank anemia				
60 μg/dL					
50 μg/dL	Reduced hemoglobin production	Overt subencephalo-neurological symptoms		Altered testicular function	Overt gastrointestinal symptoms (colic, etc.)
40 μg/dL	Increased urinary ALA and elevated coproporphyrins	Peripheral nerve dysfunction (slowed nerve conduction)			
30 μg/dL					
25-30 μg/dL	Erythrocyte protoporphyrin (EP) elevation in males				
15-20 μg/dL	Erythrocyte protoporphyrin (EP) elevation in females				
10 μg/dL	ALAD inhibition				

Abbreviations: PbB = blood lead concentrations; ALAD = δ-aminolaevulinic acid dehydratase.

earlier thought to be 'safe' for adult lead exposure. Other types of health effects occur coincident with the above overt neurological and gastrointestinal symptoms indicative of marked lead intoxication. These range from frank peripheral neuropathies to chronic nephropathy and anemia.

Toward the lower range of blood lead levels associated with overt lead intoxication, or somewhat below, less severe but important signs of impairment in normal physiological functioning in several organ systems are evident among apparently asymptomatic lead-exposed adults, including (i) slowed nerve conduction velocities indicative of peripheral nerve dysfunction (at levels as low as 30-40 μg/dL), (ii) altered testicular function (at 40-50 μg/dL), and (iii) reduced hemoglobin production (at approximately 50 μg/dL) and other signs of impaired heme synthesis evident at still lower blood lead levels. All of these effects point toward a generalized impairment of normal physiological functioning across several different organ systems, which becomes abundantly evident as blood lead levels exceed 30-40 μg/dL. Evidence for impaired heme synthesis in blood cells exists at still lower blood lead levels in adults; the medical significance of this and evidence of impairment of other biochemical processes important in cellular energetics are discussed below.

Also of much importance are studies, newly published in late 1984 and early 1985, which show statistically significant associations between elevations in systolic and diastolic blood pressure and increasing blood lead levels in adult males, even after controlling for a large number of potentially confounding variables. Blood pressure elevations are reported to be associated with PbB levels across a range of 7-≥30 μg/dL, and are projected to be associated with increased incidence of strokes, heart attacks and consequent mortality according to one of the recently published analyses. Animal toxicology studies demonstrating blood pressure increases and other cardiovascular effects experimentally induced by lead exposure provide evidence supporting the plausibility of causal links between lead and observed blood pressure effects reported in the recently published papers. Those papers and the supportive animal toxicology findings are discussed in a corrigenda (Anonymous, 1985b) for the October 1984 draft of the revised EPA criteria document (EPA, 1984).

Factors Involved in Derivation of Maximum Safe Blood Lead Levels

For children, emphasis is being placed on the discussion of (i) heme biosynthesis effects, (ii) certain other biochemical and hematological effects, and (iii) the disruption of nervous system functions. All of these appear to be among those effects of most concern for potential occurrence in association with exposure to existing US ambient air lead levels for the population group at greatest risk for lead-induced health effects (i.e. children less than or equal to 6 years of age). Emphasis is also being placed on the delineation of internal lead exposure levels, as defined mainly by blood lead levels likely associated with the occurrence of such effects. Also being discussed are characteristics of the subject effects that are of crucial importance with regard to the determination of what might reasonably be viewed as constituting 'adverse health effects' in affected human populations.

Over the years, there have been superimposed on the continuum of lead-induced biological effects various judgements as to which specific effects observed in man constitute 'adverse health effects'. Such judgements not only involve medical consensus regarding the health significance of particular effects and their clinical management, but also incorporate societal value judgements. Such societal value judgements often vary depending upon the specific overall contexts to which they are applied, such as in judging permissible exposure levels for occupational versus general population exposures to lead. For some lead exposure effects, such as severe nervous system damage resulting in death or serious medical sequelae consequent to intense lead exposure, no disagreement exists as to these being significant 'adverse health effects.' For many other effects detectable at sequentially lower levels of lead exposure, however, the demarcation lines as to which effects represent adverse health effects and the lead exposure levels at which they are accepted as occurring are neither sharp nor fixed, having changed markedly during the past several decades. That is, historically, levels of lead exposure deemed to be acceptable for either occupationally exposed persons or the general population have been steadily revised downward as more sophisticated biomedical techniques have revealed formerly unrecognized biological effects, and concern has increased about the medical and social significance of such effects.

It is difficult to provide a definitive statement of all criteria by which specific biological effects associated with any given agent can be judged to be 'adverse health effects'. Nevertheless, several criteria are currently well accepted as helping to define which effects should be viewed as 'adverse'. These include (i) impaired normal functioning of a specific tissue or organ system itself, (ii) reduced reserve capacity of that tissue or organ system in dealing with stress due to other causative agents, (iii) the reversibility/irreversibility of the particular effect(s), (iv) the relative frequency of a given effect, (v) presence of the effect in a vulnerable segment of the population, and (vi) the cumulative or aggregate impact of various effects on individual organ systems on the overall functioning and well-being of the individual.

Examples of possible uses of such criteria in evaluating lead effects can be cited for illustrative purposes. For example, impairment of heme synthesis intensifies with increasing lead exposure until hemoprotein synthesis is inhibited in many organ systems, leading to reductions in such functions as oxygen transport, cellular energetics, neurotransmitter functions, detoxification of xenobiotic agents and biosynthesis of important substances such as 1,25-dihydroxyvitamin D. In Figure 3, the far-ranging impact of lead on the body heme pool and associated disruption of many physiological processes are depicted, based on data discussed in Chapter 12 of the revised EPA (1984) criteria document. Furthermore, inspection of Figure 3 reveals effects that can be viewed as intrinsically adverse (e.g. CNS cognitive effects and peripheral nerve dysfunctions), as well as those that reduce the body's ability to cope with other forms of toxic stress, such as reduced hepatic detoxification of xenobiotics and, possibly, impairment of the immune system. The liver effect can also be cited as an example of reduced reserve capacity pertinent to consideration of the effects of lead, as the reduced capacity of the liver to detoxify certain drugs or other xenobiotic agents results from lead effects on hepatic detoxification enzyme systems.

In regard to the issue of reversibility/irreversibility of lead effects, two dimensions to the issue that really need to be considered are (i) biological reversibility or irreversibility characteristic of the particular effect in a given organism, and (ii) the generally less-recognized concept of exposure reversibility or irreversibility. Severe central nervous system damage resulting from intense, high-level lead exposure is generally accepted as an irreversible effect of lead exposure; the reversibility/irreversibility of certain more difficult to detect neurological effects occurring at lower lead exposure levels, however, remains a matter of some controversy. The concept of exposure reversibility/irreversibility can be illustrated by the case of United States urban children of low socio-economic status showing disturbances in heme biosynthesis and erythropoiesis. Biologically, these various effects may be considered reversible; the extent to which actual reversibility occurs, however, is determined by the feasibility of removing these subjects from their particular lead exposure setting. If such removal from exposure is unlikely or does not occur, then such effects will logically persist and, *de facto*, constitute essentially irreversible effects.

The issues of frequency of effects and vulnerable segments of the population in whom these effects occur are intimately related. As discussed in Chapter 13 of the revised lead document (EPA, 1984), young children--particularly inner-city children--constitute a high-risk group because they do show a high frequency of certain health effects as summarized in Table 5. The debate over which effects constitute adverse health effects in children at the lowest-observed-effect levels demonstrated for pediatric lead effects continues and has important bearing on the extent to which the maximum safe blood lead level of 30 µg/dL needs to be revised downward. Examples of some factors being considered in the debate are highlighted next.

One aspect of the debate focusses on whether relatively small enzymatic changes, such as those due to heme synthesis interference, are to be taken as adverse at low lead exposures. For example, inhibition of erythrocyte ALAD activity has been observed in humans and other mammalian species at blood lead levels even below 10-15 µg/dL, with no clear threshold evident. Correlations between erythrocyte and hepatic ALAD activity inhibition in lead workers at blood lead levels in the range of 15-56 µg/dL suggest that ALAD activity in soft tissues (e.g. brain, liver, kidney, etc.) may be inhibited at similar blood lead levels at which erythrocyte ALAD activity inhibition occurs, resulting in accumulations of ALA in both blood and soft tissues.

Some studies indicate that increases in both blood and urinary ALA occur below the currently commonly accepted blood lead level of 40 µg/dL; such increases in blood and urinary ALA are detectable in humans at PbB levels below 30 µg/dL, with no clear threshold evident down to 15-20 µg/dL, although other data exist which fail to show any relationship below 40 µg/dL blood lead. Other studies have demonstrated significant elevations in rat brain, spleen and kidney ALA levels consequent to acute or chronic lead exposure, but no clear blood lead levels can yet be specified at which such non-blood tissue ALA increases occur in humans. It is reasonable to assume, however, that ALA increases in non-blood tissues likely begin to occur at roughly the same blood lead levels associated with increases in erythrocyte ALA levels.

Lead also affects heme synthesis beyond metabolic steps involving ALA, leading to the accumulation of porphyrin in erythrocytes as the result of impaired iron insertion into the porphyrin moiety to form heme. The porphyrin acquires a zinc ion in lieu of the native iron, and the resulting accumulation of blood zinc protoporphyrin (ZPP) tightly bound to erythrocytes for their entire life (120 days) represents a commonly employed index of lead exposure for medical screening purposes. The threshold for elevation of erythrocyte protoporphyrin (EP) levels is well established as being 25-30 µg/dL in adults and approximately 15 µg/dL for young children, with significant EP elevations (greater than 1-2 standard deviations above reference normal EP mean levels) occurring in 50% of all children studied as blood lead level approaches or moderately exceeds 30 µg/dL.

Medically, small increases in EP levels have generally not been viewed as being of great concern at initial detection levels around 15-20 µg/dL in children. However, EP increases become more worrisome when markedly greater; significant EP elevations occur as blood lead levels approach and exceed 25-30 µg/dL, and additional signs of significantly deranged heme synthesis begin to appear along with indication of functional disruption of various organ systems. Previously, other such signs of significant organ system functional disruptions had only been credibly detected at PbB levels distinctly in excess of 30 µg/dL, e.g. inhibition of hemoglobin synthesis starting at 40 µg/dL and significant nervous system effects at 50-60 µg/dL. This served in 1978 as a basis for establishment by the US Centers for Disease Control (CDC, (1978) of 30 µg/dL blood lead as a criterion level for undue lead exposure for young children, and adoption by the EPA of it as the 'maximum safe' blood lead level, allowing some margin(s) of safety before reaching levels associated with inhibition of hemoglobin synthesis or nervous system deficits, in setting the 1978 NAAQS for lead.

Recently, as noted earlier, it has also been demonstrated in children that lead is negatively correlated with circulating levels of the vitamin D hormone, 1,25-dihydroxyvitamin D, with the negative association existing down to 12 µg/dL of blood lead. This effect of lead is of considerable significance on two counts: (i) altered levels of 1,25-(OH)2-vitamin D not only affect calcium homeostasis (affecting mineral metabolism, calcium as a second messenger and calcium as a mediator of cyclic nucleotide metabolism), but also likely affect its known role in immunoregulation and mediation of tumorigenesis, and (ii) the effect of lead on 1,25-$(OH)_2$-vitamin D is a particularly robust one, with blood lead levels of 30-50 μg/dL resulting in decreases in the hormone that overlap comparable degrees of decrease seen in severe kidney injury or certain genetic diseases.

Erythrocyte Py-5-N activity in children has also been demonstrated to be negatively affected by lead at exposures resulting in blood lead levels markedly below 30 μg/dL (i.e. to levels below 5 μg/dL with no evident threshold). Extensive reserve capacity exists for this blood enzyme, such that it is not markedly depleted until blood lead levels reach approximately 30-40 μg/dL, arguing for the Py-5-N effect *per se* as perhaps not being particularly adverse until such blood lead levels are reached. However, the observation of erythrocyte Py-5-N inhibition is arguably indicative of a more general, widerspread impact on pyrimidine metabolism in additional organs and tissues besides blood, such that blood lead levels lower than 30 μg/dL resulting in measurable Py-5-N inhibition in erythrocytes may be of greater medical concern when viewed from this broader perspective.

Also adding to the concern about relatively low lead exposure levels are the results of an expanding array of animal toxicology studies which demonstrate (i) persistence of lead-induced neurobehavioural alterations well into adulthood long after termination of perinatal lead exposure early in development of several mammalian species, (ii) evidence for uptake and retention of lead in neural and non-neuronal elements of the CNS, including long-term persistence in brain tissues after termination of external lead exposure and blood lead levels return to 'normal', and (iii) evidence from various *in vivo* and *in vitro* studies indicating that, at least on a subcellular-molecular level, no threshold may exist for certain neurochemical effects of lead.

Given the above new evidence that is now available, indicative of significant lead effects on nervous system functioning and other important physiological processes as PbB levels increase above 15-20 µg/dL and approach or exceed 30-40 µg/dL, the rationale for continuing to view 30 µg/dL as a 'maximum safe' blood lead level is called into question, and substantial impetus is provided for revising the criterion level downward to some level below 30 µg/dL. At present, it is difficult to identify specifically what blood lead criterion would be appropriate in view of existing information. Clearly, 30 µg/dL can no longer be seen as affording any margin of safety before blood lead levels are reached that are associated with unacceptable risk of notable adverse health effects occurring in some children. This is based on at least two grounds: (i) blood lead levels in the 30-40 µg/dL range are now known to 'mask', for some children, markedly elevated chelatable body lead burdens that are comparable with lead burdens seen in other children displaying overt signs and symptoms of lead intoxication, and (ii) blood lead levels in the 30-40 µg/dL range are also associated with the onset of deleterious effects in several organ systems which are either individually or collectively seen as being adverse.

At blood lead levels below 30 µg/dL, many of the different smaller effects reported as being associated with lead exposure might be argued as separately not being of clear medical significance, although each is indicative of interference by lead with normal physiological processes. On the other hand, the collective impact of all of the observed effects (representing potentially impaired functioning and depleted reserve capacities of many different tissues and organs) may, at some point distinctly below 30 µg/dL, be seen as representing an adverse pattern of effects worthy of avoidance with some added margin of safety. The onset of signs of detectable heme synthesis impairment in many different organ systems at blood lead levels starting around 10-15 µg/dL, along with indications of increasing degrees of pyrimidine metabolism interference and signs of altered nervous system activity, could be viewed as such a point. Or, alternatively, the collective impact of such effects might be argued as becoming sufficiently adverse to warrant avoidance (with a margin of safety) only when the various effects come to represent marked deviations from normal as PbB levels exceed 20-25 µg/dL and begin to approach the more clearly adverse 30 µg/dL level. Lastly, some medical experts argue that any deviation from normal biochemical levels or physiological functioning in any organ system should be viewed as adverse health effects to be avoided, even at PbB levels below 10 µg/dL.

The frequency of occurrence of various effects among individual, affected children at various PbB levels may have important bearing on the ultimate resolution of the above issue regarding the definition of blood lead levels associated with adverse health effects in pediatric populations. The proportion of children likely affected (i.e. responders) in terms of experiencing particular types of effects at various lead levels is also important.

Frequency of occurrence is also an important factor in viewing the significance of recently reported associations between elevated blood pressure and lead exposure in adult males. Blood pressure elevations sufficient to increase the risk of stroke and myocardial infarctions must, per se, be viewed as adverse health effects, but may occur in a relatively small proportion of lead-exposed adult males with blood lead levels below 30 µg/dL. However, the very large number (millions) of adult United States males with PbB levels in the 15-30 µg/dL range leads to the projection of large numbers (thousands) of adult males potentially being thus affected.

The ultimate impact of the above re-evaluation of 'maximum safe levels' for blood lead on future revision of the NAAQS for lead remains to be seen, because of several other factors (see Table 2) which will also need to be considered in developing the rationale for the standard. It is worth noting, however, that the US CDC (1985) has recently acted to lower the medical follow-up action level for childhood lead screening from 30 to 25 μg/dL blood lead in the presence of blood EP levels greater than or equal to 35 μg/dL. Also, recent World Health Organization (WHO, 1984) discussions have pointed toward 20-25 μg/dL as likely being seen as the PbB level associated with the onset of adverse health effects in children.

US EPA Regulation of Lead in Gasoline

Section 211 of the US Clean Air Act (USC, 1982) provides authority to the EPA Administrator to control fuels or fuel additives that (i) cause or contribute to air pollution harmful to public health or welfare, or (ii) impair the performance of emission control devices or systems. Under this statutory authority, the EPA has regulated the use of lead as a gasoline additive since 1973. More specifically, the EPA required that cars, starting with the 1975 model year, reduce lead emissions in order to avert adverse effects of lead on public health and to protect emission control equipment (catalytic converters) which is damaged or 'poisoned' by lead additives, leading to increased emissions of other noxious air pollutants (e.g. nitrogen oxides, etc). To accomplish these goals, catalytic converters requiring unleaded gasoline were installed by automobile manufacturers, and the EPA mandated under several rule-makings during 1976-82 that the lead content of leaded gasoline be reduced from over 0.5 g/L to 0.29 g/L.

These actions were based on studies showing that (i) up to 75% of the lead in leaded gasoline is emitted into the ambient air after combustion of the leaded fuel (Figure 4), (ii) ambient air lead exposure poses a threat to public health, (iii) reducing lead in gasoline would reduce blood lead levels in major population groups in the United States, thereby decreasing health impacts on such groups (especially young children), and (iv) reducing lead in gasoline would also reduce health and welfare effects due to other forms of air pollution decreased by use of catalytic converters. The effectiveness of the EPA regulations during 1976-82 is illustrated by (i) decreasing trends in leaded gasoline sales (Figure 5), (ii) decreases in the lead content of United States gasolines (Figure 6), and (iii) decreases in ambient air lead concentrations that are highly correlated with decreasing amounts of lead consumed in gasoline (Figure 7).

Relationships Between Gasoline Lead Usage and Blood Lead Levels

One of the crucial issues that has been the focal point of controversy surrounding EPA actions to reduce lead in gasoline concerns the relationship between gasoline lead usage and blood lead levels in exposed populations. Opponents of the EPA actions have argued that little or no association exists or that combustion of lead in gasoline contributes only a small proportion of blood lead in comparison with other lead exposure sources, such as lead in food. Proponents of EPA rule-making to reduce lead in gasoline, in contrast, have cited various studies as they have become available which demonstrate significant associations between gasoline lead usage and PbB levels in exposed populations.

The main data set evaluated in the 1970's as demonstrating gasoline lead - blood lead relationships in the United States was that discussed by Billick et al. (1980). Changes in PbB levels of New York City children (2-3 years

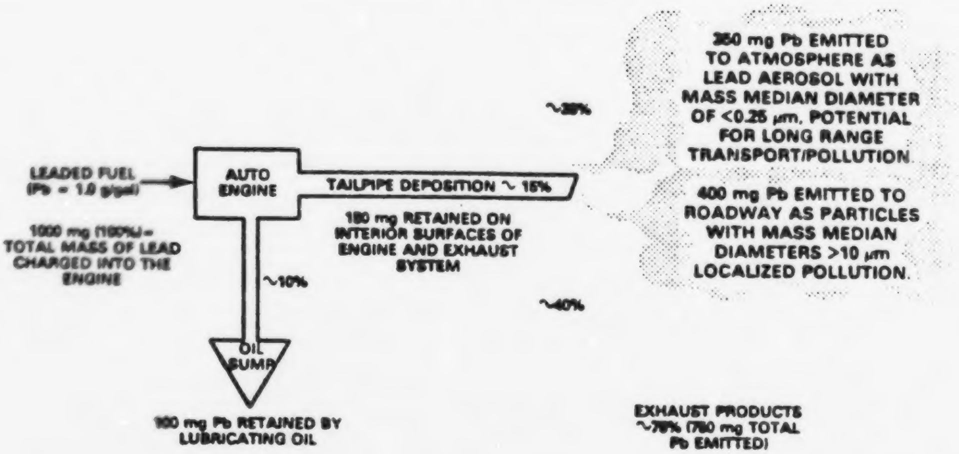
LEADED FUEL (Pb = 1.0 g/gal)
1000 mg (100%) = TOTAL MASS OF LEAD CHARGED INTO THE ENGINE
AUTO ENGINE
TAILPIPE DEPOSITION ~ 15%
150 mg RETAINED ON INTERIOR SURFACES OF ENGINE AND EXHAUST SYSTEM
~10%
OIL SUMP
100 mg Pb RETAINED BY LUBRICATING OIL
~35%
350 mg Pb EMITTED TO ATMOSPHERE AS LEAD AEROSOL WITH MASS MEDIAN DIAMETER OF <0.25 μm, POTENTIAL FOR LONG RANGE TRANSPORT/POLLUTION.
400 mg Pb EMITTED TO ROADWAY AS PARTICLES WITH MASS MEDIAN DIAMETERS >10 μm LOCALIZED POLLUTION.
~40%
EXHAUST PRODUCTS ~75% (750 mg TOTAL Pb EMITTED)

Figure 4. **Estimated lead-only emissions distribution per gallon of combusted fuel.**

old) were reported to be significantly correlated with variations in amounts of lead consumed in the New York City area from 1970 to 1976. The PbB values for the children similarly were correlated with variations in ambient air lead levels monitored at a central site in New York City. Additional evidence on the subject later emerged from a study by Rabinowitz and Needleman (1982) showing that variations in umbilical cord blood lead levels (sampled at the time of childbirth for pregnant women in Boston hospitals) were significantly correlated with variations in gasoline lead usage in Boston. More recently, Annest (1983) reported data showing highly significant correlations between nation-wide gasoline lead usage in the United States and changes in mean blood lead levels for the United States population, as determined by the Second

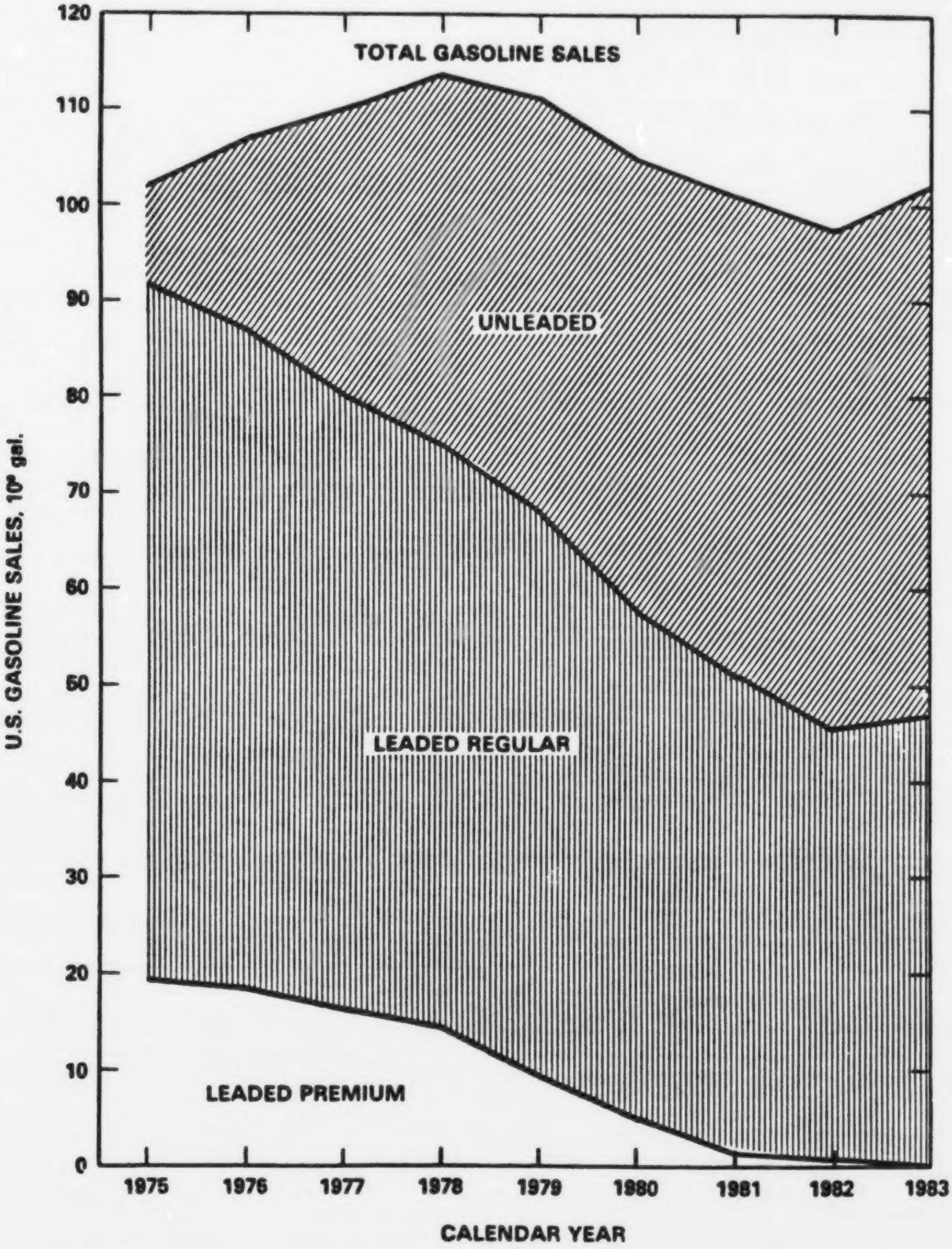

Figure 5. **Trend in U.S. gasoline sales, 1975-1983.**

Source: U.S. EPA (1984a).

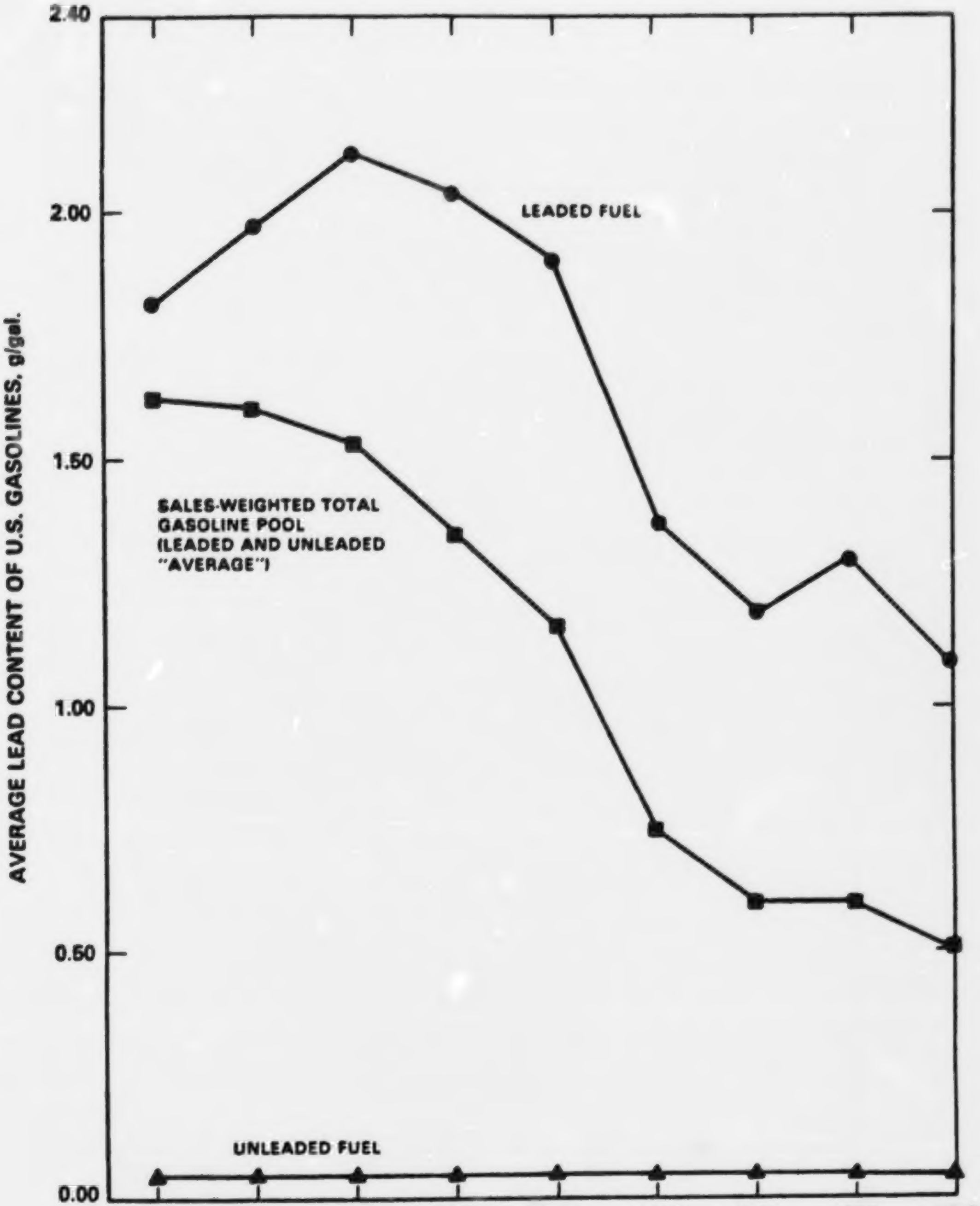

Figure 6. **Trend in lead content of U.S. gasolines, 1975-1983.**

Source: U.S. EPA (1984a).

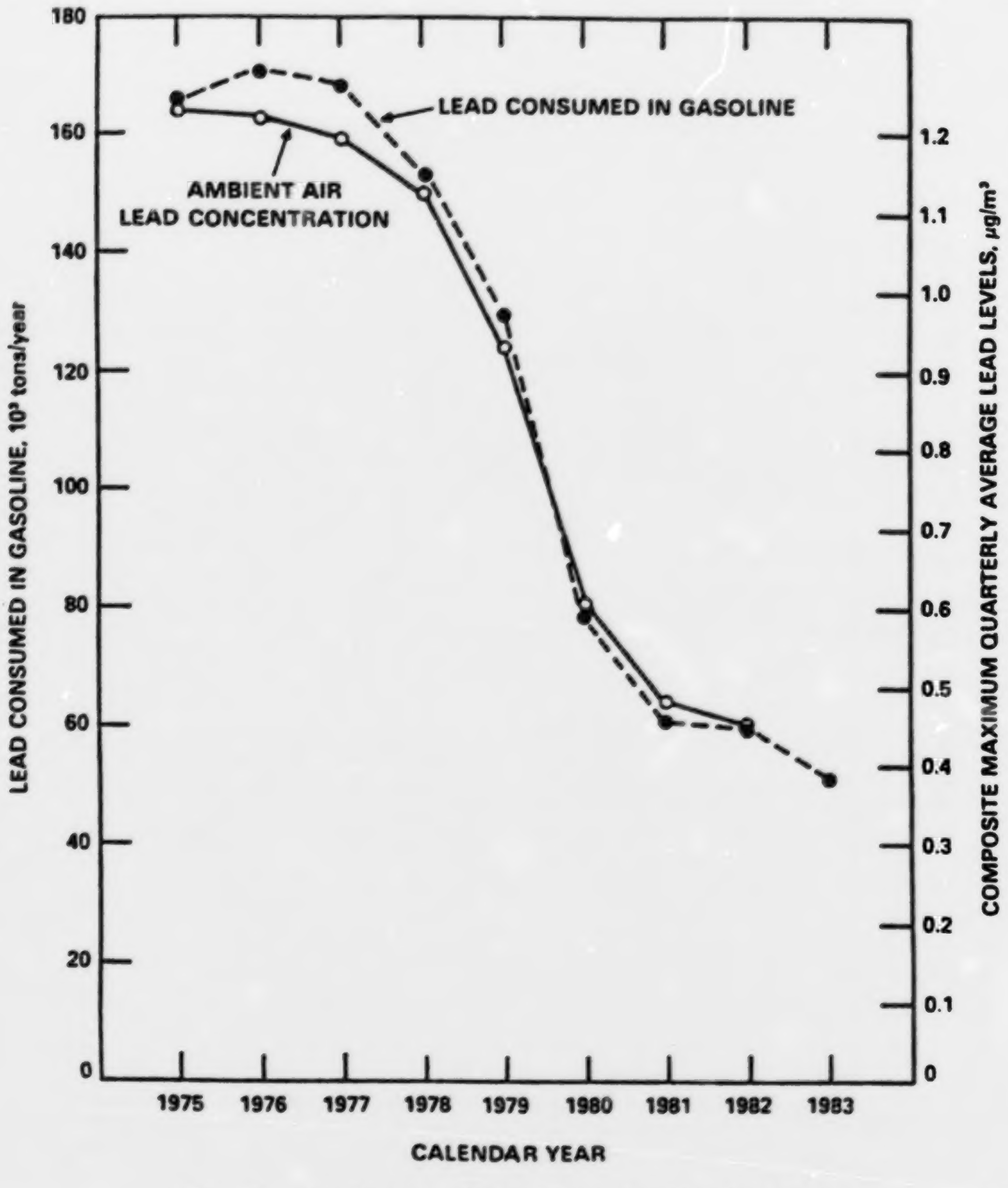

Figure 7. Lead consumed in gasoline and ambient lead concentrations, 1975-1983.

Source: U.S. EPA, 1984

National Health and Nutrition Evaluation Survey (NHANES II) carried out during 1976-80. Much controversy has been generated by these findings, with most attention being directed toward whether the entire 37% drop in PbB values between 1976 and 1980 is attributable to decreased United States gasoline usage that was markedly accelerated starting in 1977, or the possibility that decreases in other sources of lead (e.g. declines in the lead content of foodstuffs) may account for the observed decline in nation-wide average PbB levels in the United States during the NHANES II sampling period. Extensive analyses controlling for alternative sources of lead confirm that decreased gasoline lead usage was the predominant factor contributing to the decline in PbB levels.

Additional evidence of close associations between gasoline lead usage, ambient air lead and human blood lead levels has emerged from the Isotopic Lead Experiment (ILE) conducted in northern Italy and reported on by Facchetti and Geiss (1982). The ILE is a large-scale experiment whereby the ratio of stable lead isotopes (Pb-206/Pb-207) present in gasoline lead, ambient air particulate matter and adult blood lead was determined in Turin and surrounding areas of Piedmont, Italy, in 1974-75 to establish baseline values. Lead having a new Pb-206/Pb-207 isotopic ratio was introduced into the gasoline distributed throughout Piedmont, Italy, starting in 1976 and remained the predominant source of lead used in gasoline in the area until a switchback to earlier lead isotopic ratios occurred in late 1979. Changes in isotopic ratios for airborne particulate lead followed closely changes in the isotopic ratio of lead in gasoline distributed in the study area. Changes (decreases) parallel to those in the isotopic ratios for gasoline and airborne lead also occurred in blood lead levels of adults in Turin and the surrounding country-side, as well as for schoolchildren from Turin. A wide range of individual biological variation in blood lead responses to inputs of airborne lead from gasoline was well illustrated by the results reported (Facchetti and Geiss, 1982) for decreases in isotopic blood Pb-206/Pb-207 ratios for 12 adult subjects for whom repeat blood samples were obtained over the course of the study. Modelling of the ILE results indicates that a minimum of 11-24% of human blood lead concentrations in the study area was due to the gasoline with the new isotopic ratio (which may have contributed up to 40-50% of the blood lead levels in Turin if other factors are taken into account, e.g. the use of other gasoline in vehicles entering Piedmont, Italy, from outside areas).

Current Re-evaluation of EPA Gasoline Lead Regulations

The steps taken by the EPA during 1976-82 to phase down gasoline lead usage were anticipated to eventually eliminate any harmful lead exposures of the general population resulting from this source of airborne lead. Although generally effective, as noted earlier, the earlier phase-down steps have come to be recognized since 1982 as possibly not being sufficiently effective in protecting human health and welfare in the United States. This is in part due to unanticipated higher-than-expected leaded gasoline sales during the last several years due to misfuelling (use of leaded gasoline in vehicles requiring more expensive unleaded fuel) by a segment of the American public. The misfuelling results in damage to catalytic converters and resulting increases in emissions of both lead and other air pollutants.

A recent cost-benefit analysis carried out by the EPA's Office of Policy Analysis (Schwartz et al., 1985) evaluated relative benefits to be achieved by two different options for more rapid phase-down of leaded gasoline usage: (i) going to a 0.026 g/L of lead in gasoline rule, or (ii) the complete banning of all lead in gasoline sold in the United States by 1988. A variety of costs and benefits were estimated to be associated with these two options, as presented in the subject Regulatory Impact Analysis (Schwartz et al., 1985). Overall the net benefits outweigh the costs associated with the first option, even when considering only monetized benefits expected to be derived from the avoidance of costs due to health effects associated with pediatric blood lead levels of 30 µg/dL or above. Much larger gains are projected when cost/benefit ratio considerations also include benefits estimated as likely to accrue from decreasing numbers of adult males in the United States with high blood pressure due to lead exposure expected to occur if a total ban of lead in gasoline were mandated by the EPA in 1988. Based in part on the results of the above cost/benefits analysis, the EPA announced in March 1985: (i) a final rule-making requiring phase-down of lead in gasoline to 0.13 g/L by July 1985 and further phase-down to 0.026 g/L by January 1986, and (ii) a proposed rule now undergoing public comment and consideration that would require that leaded gasoline be completely banned by 1988.

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24. ROLE OF ILZRO IN ENVIRONMENTAL HEALTH RESEARCH

Jerome F. Cole

International Lead Zinc Research Organization, Inc.

For over two decades, the International Lead Zinc Research Organization, Inc., has carried out a programme of research on the effects of lead on health and on the environment. Although our research programme has been relatively small by government standards, we have made a special effort to ensure that the programmes are particularly relevant to the key issues which are of interest not only to our industry but also to government regulators. In fact, back in 1980, the US National Academy of Sciences noted:

> In summary, most of the studies ILZRO is sponsoring on lead and environmental health are on topics that were identified earlier in this report as critical information needs for making policy decisions about acceptable exposures to lead.

The existence of the programme has resulted in three key accomplishments:

1) The lead industry, through ILZRO, has made a significant contribution to the general knowledge of the effects of lead on health and the environment.

2) It has provided the ILZRO professional staff with specific background and knowledge to enable it to comment authoritatively on key environmental issues pertaining to lead.

3) It has identified a group of experts with outstanding credentials who, based on their own work and experience, provide counsel to ILZRO, governmental and industry groups.

ILZRO's research programme is developed through a variety of means. Ideas or research needs are generated or identified by our staff, working with committees from our industry. Also, ideas often come from prospective researchers or are suggested by governmental authorities.

Our staff then prepares a 'Venture Analysis' for each idea and submits them together with proposals to our various review committees. Those projects which survive the review are then funded by our Directors, often with outside financial support from non-member industries, or by governmental agencies.

It would be appropriate here to discuss finances. ILZRO is supported by the lead and zinc mining and smelting industry. Our Canadian members include Cominco, Ltd., Hudson Bay Mining and Smelting Co., Ltd., Kidd Creek Mines, Ltd., Noranda Sales Corporation, Ltd., and Sherritt Gordan Mines, Ltd. Canadian companies contribute more money to ILZRO than those of any other country in the world.

In addition to support from our members, we do work closely with consumers of our metals and, hence, receive supplementary funds from them in support of specific programmes or projects. Examples of such consumer groups include the lead acid battery industry and the producers of lead antiknock additives for gasoline.

Our staff then works with our research grantees to facilitate their research and assure appropriate review. The results are then published in the open literature. Annual summaries of each research project are also published in our ILZRO Environmental Health Research Digest.

That, in general, is how we operate. The system has evolved over the 26 years of ILZRO's existence and seems to work well. A complete description of ILZRO's methods of operation can be found in the brochure entitled 'This is ILZRO'.

The issues, as we see them, revolve around only a few key questions: (i) what are the relative contributions of various environmental sources to absorption of lead in humans? and (ii) what level of absorption of lead can be tolerated without adverse effect?

One issue has received considerable attention because it was a key finding of a group quite similar to your own. I am speaking about the UK Royal Commission on Environmental Pollution which issued a report in April of 1983 expressing the view that the margin of safety between current blood lead levels in the general population of children, and those associated with toxicity, is too low. Specifically, the Royal Commission stated:

> The average blood lead concentration in the population is about one-quarter of that at which symptoms of frank poisoning may occasionally occur.

The Royal Commission was comparing the average blood lead level in UK children (10-12 µg/dL) with the level at which it contended that frank poisoning occasionally occurs (50 µg/dL). Although we would argue that the overwhelming majority of physicians familiar with 'frank lead poisoning' would not agree that it occurs at such a relatively low blood lead level, the main point is that the Royal Commission was referring to blood lead concentrations, not to dose, on which toxicologists base safety factors. Certainly, if the dose of lead was only one-quarter of that causing frank lead poisoning, then that would be a matter of concern. However, the Royal Commission itself in Figure 4.2, page 40 of its report (Figure 1), shows quite clearly that the dose of lead (lead uptake) required to produce a blood lead level of 50 µg/dL is in the order of 15 times greater than that required to produce a blood lead concentration of 10-12 µg/dL. Therefore, the Royal Commission was guilty of illogic in not recognizing that the relationship between blood lead level and dose is not linear, but rather curvilinear. Blood lead concentration and dose were erroneously equated.

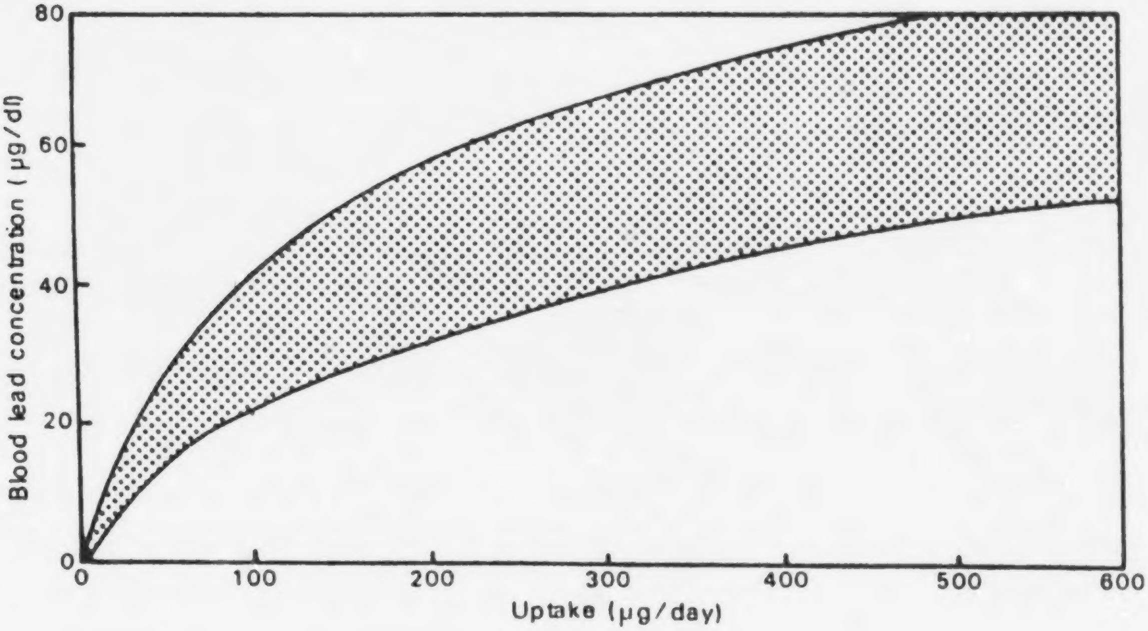

Figure 1
Relationship between blood lead concentration and total lead uptake for adults, showing the range of interpretation possible

Conclusion

My reason for raising this issue, aside from the prominence it has been given, is to note that had we and others been given the same opportunity to have input into the UK Royal Commission as you, this error probably would not have occurred.

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